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Pat nt Search

Fulltext

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 TITLE (ENGLISH): INHIBITION OF p38 KINASE ACTIVITY USING SUBSTITUTED
 HETEROCYCLIC UREAS
 TITLE (FRENCH): INHIBITION DE L'ACTIVITE DE P38 KINASE AU MOYEN D'UREES
 HETEROCYCLIQUES SUBSTITUEES
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ABSTRACT (ENGLISH):

This invention relates to the use of a group of aryl ureas in treating
 cytokine mediated
 diseases, other than cancer and proteolytic enzyme mediated diseases, other
 than cancer, and
 pharmaceutical compositions for use in such therapy.

ABSTRACT (FRENCH):

L'invention a trait a l'utilisation d'un groupe d'aryle urees pour traiter
 des maladies, autres
 que le cancer, induites par des cytokines, et des maladies, autres que le
 cancer, induites par des
 enzymes proteolytiques; et a des compositions utiles pour ce type de
 therapie.

DESCRIPTION:

io Inhibition of p38 Kinase Activity Using Substituted Heterocyclic Ureas
Field of the Invention

This invention relates to the use of a group of aryl ureas in treating cytokine mediated diseases and proteolytic enzyme mediated diseases, and pharmaceutical compositions for use in such therapy.

Background of the Invention

Two classes of effector molecules which are critical for the progression of rheumatoid arthritis are pro-inflammatory cytokines and tissue degrading proteases. Recently, a family of kinases was described which is instrumental in controlling the transcription and translation of the structural genes coding for these effector molecules.

The mitogen-activated protein (MAPK) kinase family is made up of a series of structurally related proline-directed serine/threonine kinases which are activated either by growth factors (such as EGF) and phorbol esters (ERK), or by IL-1, TNF(X or stress (p38, JNK). The kinases are responsible for the activation of a wide variety of transcription factors and proteins involved in transcriptional control of cytokine production. A pair of novel protein kinases involved in the regulation of cytokine synthesis was recently described by a group from SmithKline Beecham (Lee et al. Nature 1994, 372, 739). These enzymes were isolated based on their affinity to bond to a class of compounds, named CSAIDSs (cytokine suppressive anti-inflammatory drugs) by SKB. The CSAIDSs, bicyclic pyridinyl imidazoles, have been shown to have cytokine inhibitory activity both in vitro and in vivo. The isolated enzymes, CSBP-1 and -2 (CSAID binding protein 1 and 2) have been cloned and expressed. A murine homologue for CSBP-2, p38, has also been reported (Han et al.

Science 1994, 265, 808).

Early studies suggested that CSAIDSs function by interfering with m-RNA translational events during cytokine biosynthesis. Inhibition of p38 has been shown to inhibit both cytokine production (eg., TNF α , IL-1, IL-6, IL-8) and proteolytic enzyme production (eg., MMP-1, NRVIP-3) in vitro and/or in vivo.

Clinical studies have linked TNF(x production and/or signaling to a number of diseases including rheumatoid arthritis (Maini. J Royal Coll. Physicians London 1996, 30, 344). In addition, excessive levels of TNF α have been implicated in a wide variety of inflammatory and/or immunomodulatory diseases, including acute rheumatic fever (Yegin et al. Lancet 1997, 349, 170), bone resorption (Pacifichi et al.

J. Clin. Endocrinol. Metabol. 1997, 82, 29), postmenopausal osteoporosis (Pacifichi et al. J Bone Mineral Res. 1996, 11, 1043), sepsis (Blackwell et al. Br. J Anaesth.

1996, 77, 110), grain negative sepsis (Debets et al. Prog. Clin. Biol. Res. 1989, 308, 463), septic shock (Tracey et al. Nature 1987, 330, 662; Girardin et al. New England J Med. 1988, 319, 397), endotoxic shock (Beutler et al. Science 1985, 229, 869; Ashkenasi et al. Proc. Nat'l. Acad. Sci. USA 1991, 88, 10535), toxic shock syndrome, (Saha et al. J. Immunol. 1996, 157, 3869; Lina et al. FEMS Immunol. Med. Microbiol.

1996, 13, 81), systemic inflammatory response syndrome (Anon. Crit. Care Med. 1992, 20, 864), inflammatory bowel diseases (Stokkers et al. J. Inflamm. 1995-6, 47, 97) including Crohn's disease (van Deventer et al. Aliment. Pharmacol. Therapeut.

1996, 10 (Suppl. 2), 107; van Dullemen et al. Gastroenterology 1995, 109, 129) and ulcerative colitis (Masuda et al. J Clin. Lab. Immunol. 1995, 46, 111), Jarisch-Herxheimer reactions (Fekade et al. New England J Med 1996, 335, 311), asthma (Amrani et al. Rev. Malad. Respir. 1996, 13, 539), adult respiratory distress syndrome (Roten et al. Am. Rev. Respir. Dis. 1991, 143, 590; Suter et al. Am. Rev. Respir. Dis.

1992, 145, 1016), acute pulmonary fibrotic diseases (Pan et al. Pathol. Int. 1996, 46, 91), pulmonary sarcoidosis (Ishioka et al. Sarcoidosis Vasculitis Diffuse Lung Dis.

1996, 13, 139), allergic respiratory diseases (Casale et al. Am. J Respir. Cell Mol.

30 Biol. 1996, 152-35), silicosis (Gossart et al. J Immunol. 1996, 156, 1540; Vanhee et al. Eur. Respir. J 1995, 8, 834), coal worker's pneumoconiosis (Borm et al. Am. Rev.

Respir. Dis. 1988, 138, 1589), alveolar injury (Horinouchi et al. Am. J Respir. Cell Mol. Biol. 1996, 14, 1044), hepatic failure (Gantner et al. J Pharmacol. Exp. Therap.

WO 99/32111 4 PCT/US98/26080 Transplant. Proc. 1990, 22, 1924), lung allograft rejection (Grossman et al. Immunol.

Allergy Clin. N. Am. 1989, 9, 153) including chronic lung allograft rejection (obliterative bronchitis; LoCicero et al. J Thorac. Cardiovasc. Surg. 1990, 99, 1059), as well as complications due to total hip replacement (Cirino et al. Life

Sci. 1996, 59, 86). TNF α has also been linked to infectious diseases (review: Beutler et al. Crit.

Care Med. 1993, 21, 5423; Degre. Biotherapy 1996, 8, 219) including tuberculosis (Rook et al. Med. Malad Infect. 1996, 26] 904), *Helicobacter pylori* infection during peptic ulcer disease (Beales et al. Gastroenterology 1997, 112, 136), Chaga's disease resulting from *Trypanosoma cruzi* infection (Chandrasekar et al. Biochem. Biophys.

Res. Commun. 1996, 223, 365), effects of Shiga-like toxin resulting from *E. coli* infection (Harel et al. J Clin. Invest. 1992, 56, 40), the effects of enterotoxin A resulting from *Staphylococcus* infection (Fischer et al. J Immunol. 1990, 144, 4663), meningococcal infection (Waage et al. Lancet 1987, 355; Ossege et al. J Neurolog.

Sci. 1996, 144, 1), and infections from *Borrelia burgdorferi* (Brandt et al. Infect.

Immunol. 1990, 58, 983), *Treponema pallidum* (Chamberlin et al. Infect. Immunol.

1989, 57, 2872), cytomegalovirus (CMV; Geist et al. Am. J Respir. Cell Mol. Biol.

1997, 16, 31), influenza virus (Beutler et al. Clin. Res. 1986, 34, 491 a), Sendai virus (Goldfield et al. Proc. Nat'l. Acad. Sci. USA 1989, 87, 1490), Theiler's encephalomyelitis virus (Sierra et al. Immunology 1993, 78, 399), and the human immunodeficiency virus (HIV; Poli. Proc. Nat'l. Acad. Sci. USA 1990 87] 782; Vyakarnam et al. AIDS 1990, 4, 21; Badley et al. J Exp. Med. 1997, 185, 55).

Because inhibition of p38 leads to inhibition of TNF α production, p38 inhibitors will be useful in treatment of the above listed diseases.

A number of diseases are thought to be mediated by excess or undesired matrix-destroying metalloprotease (MMP) activity or by an imbalance in the ratio of the MMPs to the tissue inhibitors of metalloproteinases (TIMPs). These include osteoarthritis (Woessner et al. J Biol. Chem. 1984, 259, 3633), rheumatoid arthritis (Mullins et al. Biochim. Biophys. Acta 1983, 695, 117; Woolley et al. Arthritis Rheum. 1977, 20, 1231; Gravalles et al. Arthritis Rheum. 1991, 34, 1076), septic arthritis (Williams et al. Arthritis Rheum. 1990, 33, 533), tumor metastasis (Reich et al. Cancer Res. 1988, 48, 3307; Matrisian et al. Proc. Natl Acad Sci., USA 1986, 83,), periodontal diseases (Overall et al. J Periodontal Res. 1987, 22, 81), corneal

ulceration (Bums et al. Invest. OphthalmoL Vis. Sci. 1989, 30, 1569), proteinuria (Baricos et al. Biochem. J 1988, 254, 609), coronary thrombosis from atherosclerotic plaque rupture (Henney et al. Proc. Nat'l. Acad Sci., USA 1991, 88, 8154), aneurysmal aortic disease (Vine et al. Clin. Sci. 1991, 81, 233), birth control (Woessner et al. Steroids 1989, 54, 491), dystrophic epidermolysis bullosa (Kronberger et al. J Invest. Dermatol 1982, 79, 208), degenerative cartilage loss following traumatic joint injury, osteopenias mediated by Nimp activity, tempero mandibular joint disease, and demyelating diseases of the nervous system (Chantry et al. J Neurochem. 1988, 50, 688).

Because inhibition of p38 leads to inhibition of NUAP production, p38 inhibitors will be useful in treatment of the above listed diseases.

Inhibitors of p38 are active in animal models of TNF α production, including a murine lipopolysaccharide (LPS) model of TNF α production. Inhibitors of p38 are active in a number of standard animal models of inflammatory diseases, including carrageenan-induced edema in the rat paw, arachadonic acid-induced edema in the rat paw, arachadonic acid-induced peritonitis in the mouse, fetal rat long bone resorption, murine type II collagen-induced arthritis, and Freund's adjuvant-induced arthritis in the rat. Thus, inhibitors of p38 will be useful in treating diseases mediated by one or more of the above-mentioned cytokines and/or proteolytic enzymes.

The need for new therapies is especially important in the case of arthritic diseases.

The primary disabling effect of osteoarthritis, rheumatoid arthritis and septic arthritis is the progressive loss of articular cartilage and thereby normal joint function. No marketed pharmaceutical agent is able to prevent or slow this cartilage loss, although nonsteroidal antiinflammatory drugs (NSAIDs) have been given to control pain and swelling. The end result of these diseases is total loss of joint function which is only treatable by joint replacement surgery. P38 inhibitors will halt or reverse the progression of cartilage loss and obviate or delay surgical intervention.

Several patents have appeared claiming polyarylimidazoles and/or compounds containing polyarylimidazoles as inhibitors of p38 (for example, Lee et al. WO 95/07922; Adams et al. WO 95/02591; Adams et al. WO 95/13067; Adams et al. WO 95/31451). It has been reported that arylimidazoles complex to the ferric form of cytochrome P450, an, (Harris et al. Mol Eng. 1995, 5, 143, and references therein), causing concern that these compounds may display structure-related toxicity

(Howard-Martin et al. Toxicol Pathol 1987, 15, 369). Therefore, there remains a need for improved p38 inhibitors.

Summary of the Invention

This invention provides compounds, generally described as aryl 'ureas, including both aryl and heteroaryl analogues, which inhibit p38 mediated events and thus inhibit the production of cytokines (such as TNF α , IL-1 and IL-8) and proteolytic enzymes (such as MMP-1 and MMP-3). The invention also provides a method of treating a cytokine mediated disease state in humans or mammals, wherein the cytokine is one whose production is affected by p38. Examples of such cytokines include, but are not limited to TNF α , IL-1 and IL-6. The invention also provides a method of treating a protease mediated disease state in humans or mammals, wherein the protease is one whose production is affected by p38. Examples of such proteases include, but are not limited to collagenase (MMP-1) and stromelysin (MMP-3).

Accordingly, these compounds are useful therapeutic agents for such acute and chronic inflammatory and/or immunomodulatory diseases as rheumatoid arthritis, osteoarthritis, septic arthritis, rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, Jarisch-Herxheimer reactions, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic diseases, pulmonary sarcoidosis, allergic respiratory diseases, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria including Plasmodium falciparum malaria and cerebral malaria, non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's

Accordingly, the present invention is directed to a method for the treatment of diseases mediated by one or more cytokine or proteolytic enzyme produced and/or activated by a p38 mediated process, comprising administering a compound of formula I

0

1 1

A-TN.H-C-NH-B

wherein B is generally an unsubstituted or substituted, up to tricyclic, aryl or heteroaryl moiety with up to 30 carbon atoms with at least one 5 or 6 member aromatic structure containing 0-4 members of the group consisting of

nitrogen,
oxygen and sulfur. A is a heteroaryl moiety discussed in more detail below.

The aryl and heteroaryl moiety of B may contain separate cyclic structures and can include a combination of aryl, heteroaryl and cycloalkyl structures. The substituents for these aryl and heteroaryl moieties can vary widely and include halogen, hydrogen, hydrosulfide, cyano, nitro, amines and various carbon-based moieties, including those which contain one or more of Sulfur, nitrogen, oxygen and/or halogen and are discussed more particularly below.

Suitable aryl and heteroaryl moieties for B of formula I include, but are not limited to aromatic ring structures containing 4-30 carbon atoms and 1-3 rings, at least one of which is a 5-6 member aromatic ring. One or more of these rings may have 1-4 carbon atoms replaced by oxygen, nitrogen and/or sulfur atoms.

Examples of suitable aromatic ring structures include phenyl, pyridinyl, naphthyl, pyrimidinyl, benzothiazolyl, quinoline, isoquinoline, phthalimidinyl and combinations thereof, such as diphenyl ether (phenyloxyphenyl), diphenyl thioether (phenylthiophenyl), diphenyl amine (phenylaminophenyl), phenylpyridinyl ether (pyridinyloxyphenyl), pyridinylmethylphenyl, phenylpyridinyl thioether (pyridinylthiophenyl), phenylbenzothiazolyl ether (benzothiazolyloxyphenyl), phenylbenzothiazolyl thioether (benzothiazolylthiophenyl), phenylpyrimidinyl ether, phenylquinoline thioether, phenylnaphthyl ether, pyridinylnaphthyl ether, pyridinylnaphthyl thioether, and phenylphthalimidylmethyl.

Examples of suitable heteroaryl groups include, but are not limited to, 5-12 carbon-20 atom aromatic rings or ring systems containing 1-3 rings, at least one of which is aromatic, in which one or more, e.g., 1-4 carbon atoms in one or more of the rings can be replaced by oxygen, nitrogen or sulfur atoms. Each ring typically has 3-7 atoms.

For example, B can be 2- or 3-furyl, 2- or 3-thienyl, 2- or 4-triazinyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3- or 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, 1,2,3-triazol-1-, or yl, 1,2,4-triazol-1-, or yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol or yl, 1,2,4-oxadiazol or yl, 1,3,4-thiadiazol or yl, 1,2,4-oxadiazol or yl, 1,3,4-thiadiazol or yl, 1,3,4-thiadiazol or yl, 1,2,3-thiadiazol or yl, 2-, 3-, 4-, 5- or 6-2H-thiopyranyl, 2-, 3- or 4-3o 4H-thiopyranyl, 3- or 4-pyridazinyl, pyrazinyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, 1-, 2-, 3-, 4-, 5- or 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5- or 6-

7-benzoxazolyl,
 3-, 4-, 5- 6- or 7-benzisoxazolyl, 1-, 3-, 4- 5-, 6- or 7-benzothiazolyl,
 2-, 4-,] 5- 6- or
 7-benzisothiazolyl, 2-, 4-, 5-, 6- or 7-benz-1,3-oxadiazolyl, 2- 3-] 4-] 5-]
 6-] 7- or 8-
 quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, 8- isoquinolinyl, 1-, 2-, 3-, 4- or
 9-carbazolyl, 1-, 2-,
 3-] 4- 5- 6-] 7-1, 8- or 9-acridinyl, or 2-, 4-, 5- 6-, 7- or
 8-quinazolinyl, or additionally
 optionally substituted phenyl, 2- or 3-thienyl, 1,3,4-thiadiazolyl, 3-pyrryl,
 3-pyrazolyl,
 2-thiazolyl or 5-thiazolyl, etc. For example, B can be 4-methyl-phenyl,
 5-methyl
 thienyl, 4-methyl thienyl, 1-methyl pyrryl, 1-methyl pyrazolyl, 5-methyl
 thiazolyl or 5-methyl-1,2,4-thiadiazol yl.

Suitable alkyl groups and alkyl portions of groups, e.g., alkoxy, etc.
 throughout
 include methyl, ethyl, propyl, butyl, etc., including all straight-chain and
 branched
 isomers such as isopropyl, isobutyl, sec-butyl, tert-butyl, etc.

Suitable aryl groups include, for example, phenyl and 1- and 2-naphthyl.

Suitable cycloalkyl groups include cyclopropyl, cyclobutyl, cyclohexyl, etc.
 The term
 is cycloalkyl, as used herein, refers to cyclic structures with or without
 alkyl
 substituents such that, for example, C₄ cycloalkyl includes methyl
 substituted
 cyclopropyl groups as well as cyclobutyl groups. The term cycloalkyl also
 includes
 saturated heterocyclic groups.

Suitable halogens include F, Cl, Br, and/or I, from one to persubstitution
 (i.e., all H
 atoms on the group are replaced by halogen atom), being possible, mixed
 substitution
 of halogen atom types also being possible on a given moiety.

As indicated above, these ring systems can be unsubstituted or substituted by
 substituents such as halogen up to per-halosubstitution. Other suitable
 substituents for
 the moieties of B include alkyl, alkoxy, carboxy, cycloalkyl, aryl,
 heteroaryl, cyano,
 hydroxy and amine. These other substituents, generally referred to as X and
 X
 herein, include -CN, -CO₂R-, -C(O)NRR, -C(O)R, -NO₂, -OR, -SR, -NRR,
 -NR'C(O)OR, -NRC(O)R, CI-CIO alkyl, C₂-C₁₀ alkenyl, CI-C₁₀ alkoxy, C₃-C₁₀
 cycloalkyl, C₆-C₁₄ aryl, C₇-C₂₄ alkaryl, C₃-C₁₃ heteroaryl, C₄-C₂₃
 alkheteroaryl,
 substituted CI-C₁₀ alkyl, substituted C₂-C₁₀ alkenyl, substituted CI-C₁₀
 alkoxy,
 substituted C₃-C₁₀ cycloalkyl, substituted C₄-C₂₃ alkheteroaryl and -Y-Ar.

Where a substituent, X or X', is a substituted group, it is preferably
 substituted by one
 or more substituents independently selected from the group consisting of
 -CN,
 -CO₂R', -C(O)R, -C(O)NR-'R, -OR, -SR, -NRR, -NO₂, -NR₅C(O)W',

The moieties R5 and R5' are preferably independently selected from HI Cl-Clo alkyl, C.)- 3-C10 cycloalkyl, C6-C14 aryl, C3-C13 heteroaryl, C7-C24 alkaryl, C4-C23 alkheteroaryl, up to per-halosubstituted Cl-Clo alkyl, Up to per-halosubstituted C.)- 10 alkenyl, up to per-halosubstituted C3-C10 cycloalkyl, up to per-halosubstituted C6-C14 aryl and up to per-halosubstituted C3-C13 heteroaryl.

The bridging group Y is preferably , -S-, -N(R 5) _1 -(CH2)-m, _C(O)_] io -NR5C(O)NRR. -NR'C(O)-, -C(O)NR', -CH(011)-] -(CH2)mO-, -(CH2)mS-, -(CHDmN(R)_] -O(CH2)m-9 _CHXa, _CXa 2-, -S-(CH2).- and -N(R5) (CH2)m-, where ra = 1-3, and X' is halogen.

The moiety Ar is preferably a 5-10 member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z,,, wherein n1 is 0 to 3.

Each Z substituent is preferably independently selected from the group consisting of -CN, -CO2R5, =O9 _C(O)NR5R5', _C(O)_NR5. -NO29 -OR', -SR 5] _i]R5R5', _NR5C(O)ORI', -C(O)R 5, _NR5C(O)R, -SO2R 51 -SO2NR5R5', C1-C10 alkyl, C1-C10 alkoxy, C3-C10 cycloalkyl, C6-C14 aryl, C3-C13 heteroaryl, C7-C24 alkaryl, C4-C23 alkheteroaryl, substituted Cl-Clo alkyl, substituted C3-C10 cycloalkyl, substituted C7-C24 alkaryl and substituted C4-C23 alkheteroaryl. If Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of -CN, -CO2R, -C(O)NRR, =O, -OR'] -SR5. -NO2] _NR5RI -NR'C(O)R. -NWC(O)OR, Cl-Clo alkyl, Cl-Clo alkoxy, C3-C10 cycloalkyl, C-CIO heteroaryl, C6-C14 aryl, C4-C24 alkheteroaryl and C7-C24 alkaryl.

The aryl and heteroaryl moieties of B of Formula I are preferably selected from the group consisting of

0 0
R5 R5
N N
and

which are unsubstituted or substituted by halogen, up to per-halosubstitution. X is as defined above and n = 0

The aryl and heteroaryl moieties of B are more preferably of the formula IL
X
n

-Q- (Y-Qt-Zn1

wherein Y is selected from the group consisting of , -S-, -CH2-, SCH2-, -CH2S-9 -CH(OH)-, -C(O)-, -CXa2, -CXaH-, -CH2O- and -OCH2- and X' is halogen.

Q is a six member aromatic structure containing 0-2 nitrogen, substituted or unsubstituted by halogen, up to per-halosubstitution and Q1 is a mono- or bicyclic aromatic structure of 3 to 10 carbon atoms and 0-4 members of the group consisting

of N, O and S, unsubstituted or unsubstituted by halogen up to per-halosubstitution.

X, Z, n and n1 are as defined above and s = 0 or 1.

In preferred embodiments, Q is phenyl or pyridinyl, substituted or unsubstituted by halogen, up to per-halosubstitution and Q1 is selected from the group consisting of
 10 The heteroaryl moiety A of formula I is preferably selected from the group consisting

of-

R RI Rs R I

N], ,Rc N Rc Nj']'s

I I

N v

N

RI I I I

R RI R R

I RI

W]Q O'] S N N]N, ,N

I =

N J\ L N

N s

I R RI\

R R

O s

N and

s

Rb Rb

The substituent R1 preferably is selected from the group consisting of halogen, C3-C10 alkyl, C1-C13 heteroaryl, C6-C14 aryl, C7-C24 alkylaryl, C3-C10 cycloalkyl, up to per-halosubstituted C1-C10 alkyl and up to per-halosubstituted C3-C10 cycloalkyl, up to per-halosubstituted C1-C13 hetero, up to per-halosubstituted C6-C13 aryl and up to per-halosubstituted C7-C24 alkaryl.

20 The substituent R2 is preferably selected from the group consisting of H, -C(O)W2

-CO2R', C(O)NR3W'g C1-C10 alkyl, C3-C10 cycloalkyl, C7-C24 alkaryl, C4-C23 alkheteroaryl, substituted Cj-CjO alkyl, substituted C3-C10 cycloalkyl, substituted C7-

C24 alkaryl and substituted C4-C23 alkheteroaryl. Where R2 is a substituted group, it is

preferably substituted by one or more substituents independently selected from the

group consisting of -CN, - CO2R], -C(O)-NR3R3'. -NO2, -OR]] -SW, and halogen up to per-halosubstitution.

R3 and W' are preferably independently selected from the group consisting of H,

-OR]2 -SR4. -Nlft]', -C(O)R4. -CO2R4. -CMWW'] C1-C10 alkyl, C3-C10 cycloalkyl,

C6-C14 aryl, C3-C13 heteroaryl, C7-C24 alkaryl, C4-C23 alkheteroaryl, up to per-

halosubstituted C1-C10 alkyl, up to per-halosubstituted C3-C10 cycloalkyl, up

to per-halosubstituted C₆-C₁₄ aryl and up to per-halosubstituted C₃-C₁₃ heteroaryl.

R] and R]'are preferably independently selected from the group consisting of H, Cj-CIO alkyl, C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, C₃-C₁₃ heteroaryl; C₇-C₂₄ alkaryl, C₄-C₂₃ io alkheteroaryl, up to per-halosubstituted C₁-C₁₀ alkyl, up to per-halosubstituted C₃-C₁₀ cycloalkyl, up to per-halosubstituted C₆-C₁₄ aryl and up to per-halosubstituted C₃-C₁₃ heteroaryl.

Ra is preferably C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, up to per-halosubstituted C₁-C₁₀ alkyl and. up to per-halosubstituted C₃-C₁₀ cycloalkyl.

R] is preferably hydrogen or halogen.

R' is hydrogen, halogen, C₁-C₁₀ alkyl, up to per-halosubstituted C₁-C₁₀ alkyl or combines with R1 and the ring carbon atoms to which R1 and R' are bound to form a 5- or 6-membered cycloalkyl, aryl or heteroaryl ring with 0-2 members selected from O, N and S.

Preferred pyrazolyl ureas include those wherein B is 2 dichlorophenyl or of the formula II above, wherein Q is phenyl, Q1 is phenyl or pyridinyl, Y is -, -S-, -CH₂ or -SCH₂, X is CF₃, Z is OH, Cl or -NHC(O)-C₆H_{2p+1}, wherein p = 2-4, s = 0 or 1, n 0 or 1 and n1 = 0 or 1. Particular preferred pyrazolyl ureas include.

N-(3-tert-Butyl pyrazolyl)-N]-(4-(2,3-dichlorophenyl)urea;
 N-(3-tert-Butyl pyrazolyl)-N]-(3-(4-pyridinyl)thiophenyl)urea;
 N-(3-tert-Butyl pyrazolyl)-N]-(4-(4-pyridinyl)methylphenyl)urea;
 N-(3-tert-Butyl pyrazolyl)-N]-(4-(4-pyridinyl)oxyphenyl)urea;
 N-(3-tert-Butyl pyrazolyl)-N]-(4-(4-pyridinyl)thiophenyl)urea;
 N-(3-tert-Butyl pyrazolyl)-N]-(4-(4-pyridinyl)methylphenyl)urea;
 N-(1-Methyl tert-butyl pyrazolyl)-N]-(2,3-dichlorophenyl)urea;
 10 E SI A 41Au!p!i]dio lAuaqd si i,) lIXuotld
 do 'Ho ST Z JD SI X 6ZHD-
 si uiioiqm 'OAoqv II vinuLIOJ QIP JO SI a U!DJQIIItA SR= 1XIOZEXOST-E65
 Pouojolcl
 TOM (lAuoqcUxo(lAp!jAd-17)-tp)-,N-(IAIOzEJAd-g-lf4nq-i-lai-E)-N
 puuto.m OE
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 . plAppAd
 -t)-t,jX,qjouio.ionUL tu
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 troin (lXuoqdou ZUL]
 tam (lAuoqdon
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 lAqiou,-I)-N
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 -Ixqlotu(lXui
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!,oo.in-(jXuoijsdo-iojtjolg

oz

t7zjn(IXuz,qdo.ioIgoi

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-o.iolqot

.P

!uoxn(lAuoqdo.iolq-3!p-EIZ)-,,V-(IXlozujAd-g-lAlnq-;.Ia;-E-(IsqIOAxO.IPXH-Z)-
0-N

!uo.in(lXuoqd 5 i

-o-iollqoi

.P

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.p. d-

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RI P.

!po.mQAuoqdop

(IAuzqd

-lAuoq,iEooiumlSingosi-tp)-t7)-,N-(IAlozrjAd-g-lf4nq-;-iai-E-lAqioW-I)-m 9

to.mQAuz,qdoi

RI

0809Z/86S[I/JL3d I II U/66 OM

-OCpH2p+1, wherein p = 2-6, or -C(O).NH-CH3, S = 1, n = 0 or 1, and n is 0 or 1.

Particular preferred 5 isoxazolyl ureas include.

N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-hydroxyphenyl)oxyphenyl)urea;

N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-isopropoxyphenyl)oxyphenyl)urea;

N--(5-tert-Butyl isoxazolyl)-N-(4-(4-isobutoxyphenyl)oxyphenyl)urea;

N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-pentyloxyphenyl)oxyphenyl)urea;

N-(5-tert-Butyl isoxazolyl)-N]-(4-(4-methylaininocarbonylphenyl)-
oxyphenyl)urea;

N-(5-tert-Butyl isoxazolyl)-N]-(3-(4-pyridinyl)thiophenyl)urea;

N-(5-tert-Butyl isoxazolyl)-N]-(3-(4-pyridinyl)oxyphenyl)urea;

N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-pyridinyl)oxyphenyl)urea;

N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-pyridinyl)thiophenyl)urea;

N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-pyridinyl)methylphenyl)urea;

N-(5-tert-Butyl isoxazolyl)-N]-(4-(4-pyridinyl)thio (trifluoromethyl)-
phenyl)urea;

N-(5-tert-Butyl isoxazolyl)-N]-(3-(3-methyl pyridinyl)thiophenyl)urea;

N-(5-tert-Butyl isoxazolyl)-N'-(3-(3-methyl pyridinyl)oxyphenyl)urea;

N-(5-tert-Butyl isoxazolyl)-N]-(4-(3-methyl pyridinyl)oxyphenyl)urea;

N-(5-tert-Butyl isoxazolyl)-N]-(4-(3-methyl pyridinyl)thiophenyl)urea;

N-(5-tert-butyl isoxazolyl)-N-(4-(4-(2-methylcarbamoyl)pyridyl)-
oxyphenyl) urea;

N-(5-tert-butyl isoxazolyl)-N'-(3-(4-(2-methylcarbamoyl)pyridyl)-
oxyphenyl) urea;

N-(5-tert-butyl isoxazolyl)-N'-(4-(4-(2-carbainoyl)pyridyl)oxyphenyl) urea;
 N-(5-tert-butyl isoxazolyl)-N-(3-(4-(2-carbamoyl)pyridyl)oxyphenyl) urea;
 N-(5-tert-butyl isoxazolyl)-N]-(3-((4-pyridyl)fluoromethyl)phenyl) urea;
 and
 N-(5-tert-butyl isoxazolyl)-N]-(3-((4-pyridyl)oxomethyl)phenyl) urea.

Preferred 3,5-isoxazolyl ureas include those wherein B is 2,3-dichlorophenyl or of the formula 11 above, wherein Q is phenyl, Q1 is phenyl, pyridinyl or benzothiazolyl, urea;
 N-(3-tert-butyl isoxazolyl)-N]-(4-(4-pyridyl)methylphenyl) urea; and
 N-(3-tert-butyl isoxazolyl)-N]-(4-(4-methoxyphenyl)aminophenyl) urea.

Preferred thienyl ureas, furyl ureas and thiadiazolyl ureas include those wherein B is 2,3-dichlorophenyl of the formula H above, wherein Q is phenyl, Q1 is phenyl or pyridinyl, Y is , -S- or -CH₂-, Z = CH₃, OH, Cl, -O-C₂H₄ or -O-C₃H₇, s = 0 or 1, n = 0 and n1 = 0 or 1. Preferred thienyl ureas include.

N-(2-Bromo tert-butyl thienyl)-N]-(4-methylphenyl)urea;
 N-(5-tert-Butyl thienyl)-N]-(2,3-dichlorophenyl)urea;
 N-(5-tert-Butyl thienyl)-N]-(4-(4-hydroxyphenyl)oxyphenyl)urea;
 N-(5-tert-Butyl thienyl)-N'-(4-(4-ethoxyphenyl)oxyphenyl)urea;
 N-(5-tert-Butyl thienyl)-N'-(4-(4-isopropoxyphenyl)oxyphenyl)urea;
 'lXdo.id-u JO Z(EHD)HDZHD-O-'z(EHD)N
 -(O)D- 'lXlnq-u ' lf4uod-u ljf4nq-j (o)D-HN- 'lAuogd-zHD sl 9-d UloJQqAk
 9]1. 0 HN HN
 N
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 (q ol
 Ho -0 N N 0
 11 H I
 0 N
 ne-1
 :o,ulnuuoj oiqljo spunodiwoo Qpnloui Allpogloods oiotu pule QAOqv pagposop
 I Elnuuoj IviouoS jo adoos 0q) UT
 .ql!tA OM q3F
 .4M 01 S01-0101 091V UOT AUT olqL
 Po
 .P.

pucto.m(1,]uoiqdon
 U(lAu
 .p!lAd-tr)-t7)-,N-(jAuon
 . p-C-jf4nq-jaa-j-g)-N
 !roxn(lAuogciAxo(lAu!ppAd-tp)-tr)-,N-(IAuon
 . p-C-jAjng-ma;-g)-N
 !uo.m(lAuQqdAxo(1,]uippAd-E)-t7)-,N-(IAuon
 0809V86Sfl/JLDd LI I II ZC/66 OM
 C)
 Rl
 N 0
 1 1 1-
 u N -C N 0 CH3
 H H
 wherein Rl is-CH₂-t-butyl;
 d)

t-Bu
 N 0
 1 11
 In H-C-N
 R
 wherein R2 is -CH₂-CF₃, -c₂H₄-OH, -CH₂-(3-HOC₆H₄), -CH₂C(O)NH₃.

-CH₂C(O)OC₂H₅, -C₂H₄CN, or

CH

0

1 1

O-CANH

Cl c1

t-Bu

N 0 0

H 11 H 11

VN N-C-N---] C-O-C₄H₉

CH₃

f)

t-Bu

0

SL-]: 11

NH-C-NHC] -O-C] -OCH(CH₃)₂

g)

Br

N 0

11 11

s- NH-C-NH-] CH₃

and

h)

CH(CH₃)₂

CH₃

N

I 0

11

NH-C-NH

Preferred compounds also include the following thiadiazoles and thiophenes.

N-(5 -tert-butyl (1 -thia-3,4-diazolyl))-N]-(4-(4-pyridyl)oxyphenyl) urea;

N-(5-tert-butyl (I-thia-3,4-diazolyl))-N]-(3-(4-pyridyl)thiophenyl) urea;

AJoj!qn

p osruq 71ntwo ui paq osop spunoduioo

SEd ssossodqoi

.qm I L j]i

JO ULIOJ OA1 DE All-cm doio onuomi polialosi Aur sossudiumuo um Aui luosaid

oqjL

.1 .1 RUO .

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JO um ndos JO spoqjoW -SUU0j OA1 DE All-colido pur onuomi ui lsw omlotp

Re .1

weo put suoqno o!4ounmAsu ssassod I vinuuoJ JO spunodwoo mp JO ioqtunu V oz

ouo-L-oopun[0-j7-g]ojoAwqtzm

P

-861 pur (Naa) ouo-g-uou[0-C--V]oloAmqvzm -g'l '(03ava)

P

ouujoo[Z-Z-Z]ojwgez-ai -tr'l '(dVW(j) out Um

.ppAdoui jAqjoun -NN 'oulppXd

P P

IOUTUMIAxotjopAoi -ATW louiumlAqlai -ArN loui lAqjoL Te

um JO um 141P.Iod Io gz
P P
um uoloiduio4guTsLmosoipsugonssuoi oummounuukmuiolunbptm'tuniuoumm
Re it,
poinijisps Di tuam put Di ildip Sui njout 4sos-eq onm&o JO silts ppr SE 110M
Re Re . P
SE 'U01lro U.Mruounur QTjj 6(z -egio z UD I z 2w 6 3) SUOTIVO qpro oullmlu
M.10 -gm
ill o)suoi oouilmUtftu luoosllrsst)lqons'sosugomBiouijosllrsp!o-e))pnloui
+4 .110 . TO
silts olquidoom Allmilnooleumqd 6uoi!ppv ul -ppr Di opurTu put 'plor
wjQorlxUQqd oz
4ppe oilAoijsvs Ippe oiozuq 'ppv walrui Ippr oLmumj 4ppr oluloons 'plot
oilexo
'plov Di oul 'plor oL
.4p 6plou oLmlml Ippr oiltnu 4ppu Di oovoionu]n 4ppe 01 ODE 'P!3v
omoqdlms 'plou oruoqdlmsoueqlztu lppv ouoqdsod'plo-c o]mqdlms lppE
wT.UoiqoipAq
4ppe ouolqooipAq SE qons 'splov oungio pur onmi?.ioui JO silts 3isug opnjoui
put
w oqi ui pQllqs asoill ol umou)l llom On silts olqvidooov AllminoovuLmqd
Qlqul!nS -I gi
rlnuuoj JO silts olquidooor XllumjnoovuLmqd ol poloom OSIE St U01jU3AU1
TUOsaid Qqj
P

TOM (lXuoqd/ixo(lXuoqd,]xodoidosi-i7)-.V)-,N-(IXuan]4
put tom (lXuoqdXxo(lAuoqdAxoqlt-tv)-i7)-, N-(IAuoi
tom (lAuzqdAxo(lXuoqcfAxoqloui-i7)-t7)-,V-(IKuou
01
to.in
tom QAuoqdoiolt4m -E'Z)-,N-(lAui
.P
tain (lAuoqdlAqlow(lAppAd-i7)-t7)-,N-(IAuou 44
nq-p9j-g)-N
!ro.m (lAuoqdoi
.qjQAppXd-t7)-tp)-,N-(lAui
.qj-E-jfqng-maj-g)-N
toin (lXuoqcUxo(lAppAd-t7)-V)-,N-(IAuou 44
!-eojn
(lAuoqd,]xo(lXuoqdlAqlou.i-t7)-E)-,N-((IXlozuip-17'E-ioi
toin
(Ixuoclxxo(lxuzqcuxoqlatu-tF)-E)-,N-((IXlozui -j7IC-tu
.P p-l)-Z-114nq-ma;-g)-)V
0809V86Sf1/.L3d 0z I II U/66 OM

General Preparative Methods

The compounds of Formula I may be prepared by use of known chemical reactions and procedures, some from starting materials which are commercially available.

Nevertheless, the following general preparative methods are presented to aid one of skill in the art in synthesizing the inhibitors, with more detailed particular examples being presented in the experimental section describing the working examples.

Heterocyclic amines may be synthesized utilizing known methodology (Katritzky, et

al. Comprehensive Heterocyclic Chemistry; Pergamon Press: Oxford, UK (1984).

March. Advanced Organic Chemistry, 3d Ed.; John Wiley: New York (1985)). For

example, 3-substituted aminoisoxazoles (3) are available by the reaction of hydroxylamine with an α -cyanoketone (2), as shown in Scheme I. Cyanoketone 2, in turn, is available from the reaction of acetamido ion with an appropriate acyl derivative, such as an ester, an acid halide, or an acid anhydride. Reaction of an α -cyanoketone with hydrazine ($R_2=H$) or a monosubstituted hydrazine affords the 3-substituted- or 1,3-disubstituted aminopyrazole (5). Pyrazoles unsubstituted at N-1 ($R_1=H$) may be acylated at N-1, for example using di-*tert*-butyl dicarbonate, to give pyrazole 7. Similarly, reaction of nitrile 8 with a thioacetate ester gives the 5-substituted amino thiophenecarboxylate (9, Ishizaki et al. JP 6025221).

Decarboxylation of ester 9 may be achieved by protection of the amine, for example as the *tert*-butoxy (BOC) carbamate (10), followed by saponification and treatment with acid. When BOC protection is used, decarboxylation may be accompanied by deprotection, giving the substituted 3-thiopheneammonium salt 11. Alternatively, ammonium salt 11 may be directly generated through saponification of ester 9 followed by treatment with acid.

CH₃CN

R'

1) base

2) H₂NOH·HCl

R₁ X NH₂

3

R₁

NHNH₂ 4

CN N]

R₁]NINH₂ 0

RO)] X

5

2 R₁

R H >

K

R₁ N NH₂

R' HS., .CO₂R 0 R

cl)] =] S 7

CN -] INH₂

8 CO₂R

9

1) OH- 0 0

2) H >])])1]0-]]

0 0

Ir

R' R₁

1) OH-

st] 14 2) H+

NH₃+ NHBOC

CO₂R

11 10

Scheme 1. Selected General Methods for Heterocyclic Amine Synthesis

Substituted anilines may be generated using standard methods (March. Advanced

Organic Chemistry, 3d Ed.; John Wiley: New York (1985). Larock. Comprehensive Organic Transformations; VCH Publishers: New York (1989)). As shown in Scheme II, aryl amines are commonly synthesized by reduction of nitroaryls using a metal catalyst, such as Ni, Pd, or Pt, and H₂ or a hydride transfer agent, such as formate, cyclohexadiene, or a borohydride (Rylander. Hydrogenation Methods; Academic Press: London, UK (1985)). Nitroaryls may also be directly reduced using a strong hydride source, such as LiAlH₄ (Seyden-Penne. Reductions by the Alumino- and Borohydrides in Organic Synthesis; VCH Publishers: New York (1991)), or using a zero valent metal, such as Fe, Sn or Ca, often in acidic media. Many methods exist

H₂ / catalyst

(eg. Ni, Pd, Pt)

ArNO₂ [H-] \rightarrow ArNH₂

(eg. Fe, Sn, Ca)

Scheme 11 Reduction of Nitroaryls to Aryl Amines

Nitroaryls are commonly formed by electrophilic aromatic nitration using HNO₃, or

an alternative NO₂⁺ source. Nitroaryls may be further elaborated prior to reduction.

Thus, nitroaryls substituted with

HNO₃

Ar-H ON- ArNO₂

or potential leaving groups (eg. F, Cl, Br, etc.) may undergo substitution reactions on

treatment with nucleophiles, such as thiolate (exemplified in Scheme III) or phenoxide. Nitroaryls may also undergo Ullman-type coupling reactions (Scheme 12)

ArNO₂ ArSH

R F

base

12 ArNO₂

S-Ar

R::D-

ArNO₂ Br-Ar 13

SH

CuO / base

14

Scheme III Selected Nucleophilic Aromatic Substitution using Nitroaryls

As shown in Scheme IV, urea formation may involve reaction of a heteroaryl isocyanate (17) with an aryl amine (16). The heteroaryl isocyanate may be synthesized from a heteroaryl amine by treatment with phosgene or a phosgene equivalent, such as trichloromethyl chloroformate (diphosgene), bis(trichloromethyl)

carbonate (triphosgene), or NN'-carbonyldiimidazole (CDI). The isocyanate may also be derived from a heterocyclic carboxylic acid derivative, such as an ester, an

acid halide or an anhydride by a Curtius-type rearrangement. Thus, reaction of acid

derivative 21 with an azide source, followed by rearrangement affords the isocyanate.

The corresponding carboxylic acid (22) may also be subjected to Curtius-type rearrangements using diphenylphosphoryl azide (DPPA) or a similar reagent. A urea

may also be generated from the reaction of an aryl isocyanate (20) with a heterocyclic amine.

Het-NH₂ 16 H₂N-Ar 19

COC12 COC12

H₂N-Ar 0 Het-NH₂

Het-NCO)P. Het-,)] Ar oW - OCN-Ar

N N'

17 H H 20

18

N3 PPA N3 PPA

0 0 0 0

HetAX HeClkOH X-kAr HO)]Ar

22 23 24

io Scheme IV Selected Methods of Urea Formation (Het = heterocycle)

1-Amino heterocyclic carboxylic esters (exemplified with thiophene 9, Scheme V)

may be converted into an isatoic-like anhydride (25) through saponification, followed

by treatment with phosgene or a phosgene equivalent. Reaction of anhydride 25 with

an aryl amine can generate acid 26 which may spontaneously decarboxylate, or may

be isolated. If isolated, decarboxylation of acid 26 may be induced upon heating.

RI

R

1) OH-

S 00

_]_NH₂ 2) COC12 NH 25

R02C O

9

H₂N-Ar

R

R

0 A 0

S a- N 'K N' Ar 49 S)] Ar

H H N N'

H02C H H

27 _J

26

Scheme V Urea Formation via Isatoic-like Anhydrides

Finally, ureas may be further manipulated using methods familiar to those skilled in the art.

The invention also includes pharmaceutical compositions including a compound of

this invention as described above, or a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier.

io The compounds may be administered orally, topically, parenterally, by inhalation or spray, sublingually, or rectally or vaginally in dosage unit formulations. The term

'administration by injection' includes intravenous, intramuscular, subcutaneous and

parenteral injections, as well as use of infusion techniques. Dermal administration

may include topical application or transdermal administration. One or more

compounds may be present in association with one or more non-toxic pharmaceutically acceptable carriers and if desired other active ingredients.

Compositions intended for oral use may be prepared according to any suitable method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from the group consisting of diluents, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; and binding agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. These compounds may also be prepared in solid, rapidly released form.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions containing the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions may also be used. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene

sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

The compounds may also be in the form of non-aqueous liquid formulations, e.g., oily suspensions which may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or peanut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oil phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The compounds may also be administered in the form of suppositories for

rectal

administration of the drug. These compositions can be prepared by mixing the drug

with a suitable non-irritating excipient which is solid at ordinary temperatures but

Compounds of the invention may also be administered transdermally using methods

known to those skilled in the art (see, for example: Chien; Transdermal Controlled

Systemic Medications; Marcel Dekker, Inc.; 1987. Lipp et al. W094/04157 3Mar94). For example, a solution or suspension of a compound of Formula I in a

suitable volatile solvent optionally containing penetration enhancing agents can be

io combined with additional additives known to those skilled in the art, such as matrix

materials and bacteriocides. After sterilization, the resulting mixture can be

formulated following known procedures into dosage forms. In addition, on treatment

with emulsifying agents and water, a solution or suspension of a compound of Formula I may be formulated into a lotion or salve.

Suitable solvents for processing transdermal delivery systems are known to those

skilled in the art, and include lower alcohols such as ethanol or isopropyl alcohol,

lower ketones such as acetone, lower carboxylic acid esters such as ethyl acetate,

polar ethers such as tetrahydrofuran, lower hydrocarbons such as hexane, cyclohexane

or benzene, or halogenated hydrocarbons such as dichloromethane, chloroform, trichlorotrifluoroethane, or trichlorofluoroethane. Suitable solvents may also include

mixtures of one or more materials selected from lower alcohols, lower ketones, lower

carboxylic acid esters, polar ethers, lower hydrocarbons, halogenated hydrocarbons.

Suitable penetration enhancing materials for transdermal delivery system are known

to those skilled in the art, and include, for example, monohydroxy or polyhydroxy

alcohols such as ethanol, propylene glycol or benzyl alcohol, saturated or unsaturated

C8-C18 fatty alcohols such as lauryl alcohol or cetyl alcohol, saturated or unsaturated

C8-C18 fatty acids such as stearic acid, saturated or unsaturated fatty esters with up to

30 24 carbons such as methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl isobutyl

tertbutyl or monoglycerin esters of acetic acid, capronic acid, lauric acid, myristinic

acid, stearic acid, or palmitic acid, or diesters of saturated or unsaturated dicarboxylic

acids with a total of up to 24 carbons such as diisopropyl adipate, diisobutyl adipate,

diisopropyl sebacate, diisopropyl maleate, or diisopropyl fumarate. Additional

Suitable binding materials for transdermal delivery systems are known to

those skilled in the art and include polyacrylates, silicones, polyurethanes, block polymers, styrenebutadiene copolymers, and natural and synthetic rubbers. Cellulose ethers, derivatized polyethylenes, and silicates may also be used as matrix components.

Additional additives, such as viscous resins or oils may be added to increase the viscosity of the matrix.

For all regimens of use disclosed herein for compounds of Formula 1, the daily oral dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily rectal dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/Kg. The daily inhalation dosage regimen will preferably be from 0.01 to 10 mg/Kg of total body weight.

It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when administering therapeutics.

It will also be understood, however, that the specific dose level for any given patient will depend upon a variety of factors, including, the activity of the specific compound employed, the age of the patient, the body weight of the patient, the general health of the patient, the gender of the patient, the diet of the patient, time of administration, route of administration, rate of excretion, drug combinations, and the severity of the condition undergoing therapy.

It will be further appreciated by one skilled in the art that the optimal course of treatment, ie, the mode of treatment and the daily number of doses of a compound of Formulae I or a pharmaceutically acceptable salt thereof given for a defined number of days, can be ascertained by those skilled in the art using conventional

course of
treatment tests.

The entire disclosure of all applications, patents and publications cited above and below are hereby incorporated by reference, including provisional application Attorney Docket No. Bayer I 1 VI, filed December 22, 1997, as SN 08/995,750, and was converted on December 22, 1998.

The following examples are for illustrative purposes only and are not intended, nor should they be construed to limit the invention in any way.

EXAMPLES

All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of dry argon or dry nitrogen, and were stirred magnetically unless otherwise indicated. Sensitive liquids and solutions were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Unless otherwise stated, the term 'concentration under reduced pressure' refers to use of a Buchi rotary evaporator at approximately 15 mmHg.

All temperatures are reported uncorrected in degrees Celsius (°C). Unless otherwise indicated, all parts and percentages are by weight.

Commercial grade reagents and solvents were used without further purification.

Thin-layer chromatography (TLC) was performed on Whatman pre-coated glass-backed silica gel 60A F-254 250 gm plates. Visualization of plates was effected by one or more of the following techniques: (a) ultraviolet illumination, (b) exposure to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating, (d) immersion of the plate in a cerium sulfate solution followed by heating, and/or (e) immersion of the plate in an acidic ethanol solution of 2,4-dinitrophenylhydrazine followed by heating. Column chromatography (flash chromatography) was performed using 230-400 mesh EM Science silica gel.

Melting points (mp) were determined using a Thomas-Hoover melting point apparatus or a Mettler FP66 automated melting point apparatus and are uncorrected. Fourier

transform infrared spectra were obtained using a Mattson 4020 Galaxy Series spectrophotometer. Proton (¹H) nuclear magnetic resonance (NMR) spectra were measured with a General Electric GN-Omega 300 (300 MHz) spectrometer with either Me₄Si (δ 0.00) or residual protonated solvent (CHCl₃ δ 7.26; MeOH δ 3.30; DMSO-d₆ δ 2.49) as standard. Carbon (¹³C) NMR spectra were measured with a General Electric GN-Omega 300 (75 MHz) spectrometer with solvent (CDCl₃ δ 77.0;

MeOD-d3; 5 49.0; DMSO-d6 8 39.5) as standard. Low resolution mass spectra (MS) and high resolution mass spectra (HRMS) were either obtained as electron impact (EI) mass spectra or as fast atom bombardment (FAB) mass spectra. Electron impact mass spectra (EI-MS) were obtained with a Hewlett Packard 5989A mass spectrometer. Elemental analyses were conducted by Robertson Microlit Labs, Madison NJ. All ureas displayed NMR spectra, LRMS and either elemental analysis or HRMS consistent with assigned structures.

List of Abbreviations and Acronyms.

AcOH acetic acid
 anh anhydrous
 BOC tert-butoxycarbonyl
 conc concentrated
 3o dec decomposition
 DMPU 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
 DMF NN-dimethylformamide
 DMSO dimethylsulfoxide
 DPPA diphenylphosphoryl azide
 MeOH methanol
 pet. ether petroleum ether (boiling range 30-60 °C)
 THF tetrahydrofuran
 TFA trifluoroacetic acid
 io Tf trifluoromethanesulfonyl
 A* General Methods for Synthesis of Heterocyclic Amines
 A2. General Synthesis of 5-Amino alkylisoxazoles

0

CN

Step 1. 3-Oxo methylpentanenitrile: A slurry of sodium hydride (60% in mineral oil; 10.3 g, 258 mmol) in benzene (52 mL) was warmed to 80 °C for 15 min., then a solution of acetonitrile (13.5 mL, 258 mmol) in benzene (52 mL) was added dropwise via addition funnel followed by a solution of ethyl isobutyrate (15 g, 129 mmol) in benzene (52 mL). The reaction mixture was heated overnight, then cooled with an ice water bath and quenched by addition of 2-propanol (50 mL) followed by water (50 mL) via addition funnel. The organic layer was separated and set aside. EtOAc (100 mL) was added to the aqueous layer and the resulting mixture was acidified to approximately pH 1 (conc. HCl) with stirring. The resulting aqueous layer was extracted with EtOAc (2 x 100 mL). The organic layers were combined with the original organic layer, dried (MgSO₄), and concentrated in vacuo to give the α-cyanoketone as a yellow oil which was used in the next step without further purification.

N

0 NH₂

9z

GS) Clog 6(HZ's Jq) Zlog '(HZ'ZH 6*9=0) V017 '(HZ'ZH 6*9--F'I) Z87 IH6 6s) Ell 2 (9P-0SWG) -dM-H, IC-OfU (Qu-9xQlq %0L/0V0la %oz) DriL :(%OE 'S g*z) jonpaid pansop otp pioj7 ol (auuxoq/0zja) pol-em-41g

SUIA ligualmi gm nsai oiql p
 .11 U'u (QU13XOq %0C/3V0la %OL 01 Zu'uxOlq %09/DV019
 %0tF tuo-U lu0jp,9B) voij!s JO ptd v q2nojql pojollU sm onppai Qqj pur
 amssaid oz
 POMPO-I WM P0124MMOO Sum ojmX!Tu oqj, -uopovai ololdwoout pomoqs sisspur
 DrIj, lq3'r m U!
 .qM JOUP lq2lLUQAO oim-modiml xnUoi oqj 1-c polroq sm (I 001) H019
 QOUru 6%St7 T 19-0 Oulzu-Tkq 1,KqlQ0urX0-Z PUB (IOUItu c*.vty' 9*g) 1.
 luodoxo
 2? a L4!UQUu
 -E-jXqiotui -174tp JO uoi los V :alozuiXd(lXqlaouui;-Z)-l-li]4nq-lial-E-
 ouimv-s
 .P Rn
 ON
 zHN N
 saj0zvlAdjA3jjv-E-jS3jju- I-ouitaV-S jo uoi viudajd aqj ioj poqlaN junuaf)
 oEV
 LZI (Q0u9Punq'u 10-0 zlzu SW-aVj !(HI 's) VV*9 6(HZ 's) 080-V '(HI 'zH O*L=r
 6lclos)
 ZL'Z IH9 4zH O*L=f 4P) UT P (9P-0SWG) UKM-H, !61]0 (lIdzHD %96/0uOl03'0 01
 %9) --d DPIJL !Do 99-E9 du-I :(%OL 'S E& II) MlOs m0110A V sfe 010zox0s'
 PAIMP 0T.11
 pjojju 01 (zldzHD %06/Qu0103P %0 1) voij!s JO pud u qSnojqq paiollu sum pps
 mollox
 Allo Sui Insai aqL -onom uz polaquamw pim 1(tYOSEW) pou
 p wom sioXvI mm&o
 pouiquoo oq.L -2ui ow jnoqjjm (qw 001 x 0 ElDHD Wm PlOv4xa XI0j-u!P0umul
 sTtA ojmxiui uoilonj uLmm oql -11o molloX osuop ssol r oonpaid ol sinoq g-Z
 ioj g.
 D. og ir pol-niq sTm uoi los molloX SuilInsai oqL -2uLulls oli
 Rn qm ojjjj!uourjuodjAlqj0w
 -t-oxo-C optuo JO uoT os v olu! pamod s-em uoi los Sui Insai oip pu-e (qm CL)
 .lni Rn .1
 101M ul QOUItu gtP9 '2 6* 9Z) HGON JO uOllnlOs P100 031 uu 01 POPPE AVA0ls MA
 QOUru
 8trl 'S E*01) ap!jojgoojpAq ouiumjAxoipAH :ajozvxosijSdoidosi-E-omtuV-S *Z
 dals
 0809V86Sfi/13d I II U/66 OM
 A 4. Synthesis of 3-Amino alkylthiophenes-
 A4a. Synthesis of 3-Amino alkylthiophenes by Thermal Decarboxylation of
 Thiophenecarboxylic Acids
 NH
 0]]o
 Step 1. 7-tert-Butyl-2H-thieno[3,2-d]oxazine-2,4(1H)-dione: A mixture of
 methyl
 3-amino tert-butylthiophenecarboxylate (7.5 g, 35.2 mmol) and KOH (5.92 g) in
 MeOH (24 mL) and water (24 mL) was stirred at 90 °C for 6 h. The reaction
 mixture
 was concentrated under reduced pressure and the residue was dissolved in
 water (600
 mL). Phosgene (20% in toluene, 70 mL) was added dropwise over a 2 h period.
 The
 io resulting mixture was stirred at room temperature overnight and the
 resulting
 precipitate was triturated (acetone) to afford the desired anhydride (5.78 g,
 73%): 'H.
 NMR (CDCl3) δ 1.38 (s, 9H), 2.48 (s, 1H), 6.75 (s, 1H); FAB-MS mlz (rel
 abundance)
 226 ((M+H)+g 100%).

O

N N

HOO H H

Step 2. N-(5-tert-Butyl carboxy thienyl)-N]-(4-(4-pyridinylmethyl)phenyl)-urea: A solution of 7-tert-butyl-2H-thieno[3,2-d]oxazine-2,4(1H)-dione (0.176 g,

0.78 mmol) and 4-(4-pyridinylmethyl)aniline (0.144 g, 0.78 mmol) in THF (5 mL)

was heated at the reflux temp. for 25 h. After cooling to room temp., the resulting

solid was triturated with Et₂O to afford the desired urea (0.25 g, 78%): mp 187-189

OC; TLC (50% EtOAc/50% pet. ether) R_f 0.04; ¹H-NMR (DMSO-d₆) 8 1.34 (s, 9H), 3.90 (s, 2H), 7.15 (d, J=7Hz, 2H), 7.20 (d, J=3 Hz, 2H), 7.40 (d, J=7 Hz, 2H), 7.80 (s

1H), 8.45 (dq J=3 Hz, 2H) 9.55 (s, 1H), 9.85 (s, 1H), 12.50 (br s, 1H);

FAB-MS m/z

(rel abundance) 41 0 ((N₄+H) ⁺; 20%).

N

N N

H H

Step 3. N-(5-tert-Butyl thienyl)-N]-(4-(4-pyridinylmethyl)phenyl)urea: A vial containing N-(5-tert-butyl carboxy thienyl)-N]-(4-(4-pyridinylmethyl)phenyl)-urea (0.068 g, 0.15 mmol) was heated to 199 °C in an oil bath. After gas evolution

ceased, the material was cooled and purified by preparative FIPLC (C-18 column;

gradient from 20% CH₃CN/79.9% H₂O/0- 1 % TFA to 99.9% H₂O/0- 1 % TFA) to give the desired product (0.024 g, 43%): TLC (50% EtOAc/50% pet. ether) R_f 0.18;

¹H-

NMR (DMSO-d₆) 8 1.33 (s, 9H), 4.12 (s, 2H), 6.77 (s, 1H), 6.95 (s, 1H), 7.17 (d, J=9

Hz, 2H), 7.48 (d, J=9 Hz, 2H), 7.69 (d, J=7 Hz, 1H), 8.58 (s, 1H), 8.68 (d, J=7 Hz,

io 2H)q 8.75 (s, 1H); EI-MS m/z 365 W).

A4b. Synthesis 3-Amino alkylthiophenes from 3-Amino alkyl thiophene-carboxylate esters

NH₃⁺ Cl⁻

5-tert-Butyl thiopheneammonium Chloride: To a solution of methyl 3-amino tert-butyl thiophene-carboxylate (5.07 gq 23.8 mmol, 1.0 equiv) in EtOH (150 mL)

was added NaOH (2.0 g, 50 mmol, 2.1 equiv). The resulting solution was heated at

the reflux temp. for 2.25 h. A cone. HO solution (approximately 10 mL) was added

dropwise with stirring and the evolution of gas was observed. Stirring was continued

for 1 h, then the solution was concentrated under reduced pressure. The white residue

was suspended in EtOAc (150 mL) and a saturated NaHCO₃ solution (150 mL) was added to dissolve. The organic layer was washed with water (150 mL) and a saturated

NaCl solution (150 mL), dried (Na₂SO₄). and concentrated under reduced pressure to

give the desired ammonium salt as a yellow oil (3.69 gq 100%). This material was

used directly in urea formation without further purification.

A4c, Synthesis 3-Amino alkylthiophenes from N-BOC 3-Amino alkyl thiophenecarboxylate esters

0

NI_kO_Ik

MeO2 H

Step 1. Methyl 3-(tert-Butoxycarbonylamino) tert-butyl thiophenecarboxylate: To a solution of methyl 3-amino tert-butyl thiophenecarboxylate (150 g, 0.70 mol) in pyridine (2.8 L) at 5 °C was added di-tert-butyl dicarbonate (171.08 g, 0.78 mol, 1.1 equiv) and NN-dimethylaminopyridine (86 g, 0.70 mol, 1.00 equiv) and the resulting mixture was stirred at room temp for 7 d. The resulting dark solution was concentrated under reduced pressure (approximately 0.4 mmHg) at approximately 20 °C. The resulting red solids were dissolved in CH₂Cl₂ (3 L) and sequentially washed with a 1 M H₃PO₄ solution (2 x 750 mL), a saturated NaHCO₃ solution (800 mL) and a saturated NaCl solution (2 x 800 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The resulting orange solids were dissolved in abs. EtOH (2 L) by warming to 49 °C, then treated with water (500 mL) to afford the desired product as an off-white solid (163 g, 74%): ¹H-NMR (CDCl₃) δ 1.38 (s, 9H), 1.51 (s, 9H), 3.84 (s, 3H), 7.68 (s, 1H), 9.35 (br s, 1H); FAB-MS m/z (rel abundance) 314 ((M+H)⁺) 45%.

0

N-]ko_]_k

HO2 H

Step 2. 3-(tert-Butoxycarbonylamino) tert-butyl thiophenecarboxylic Acid.

2o To a solution of methyl 3-(tert-butoxycarbonylamino) tert-butyl thiophenecarboxylate (90.0 g, 0.287 mol) in THF (630 mL) and MeOH (630 mL) was added a solution of NaOH (42.5 g, 1.06 mL) in water (630 mL). The resulting mixture was heated at 60 °C for 2 h, concentrated to approximately 700 mL under reduced pressure, and cooled to 0 °C. The pH was adjusted to approximately 7 with a 1.0 N HCl solution (approximately 1 L) while maintaining the internal temperature at approximately 0 °C. The resulting mixture was treated with EtOAc (4 L). The pH was adjusted to approximately 2 with a 1.0 N HCl solution (500 mL). The organic phase was washed with a saturated NaCl solution (4 x 1.5 L), dried (Na₂SO₄), and concentrated to approximately 200 mL under reduced pressure. The residue was treated with hexane (1 L) to form a light pink (41.6 g). Resubmission of the mother liquor to the concentration-precipitation protocol afforded additional product (38.4 g, 93% total yield): ¹H-NMR (CDCl₃) δ 1.94 (s, 9H), 1.54 (s, 9H), 7.73 (s, 1H), 9.19 (br s, 1H); FAB-MS m/z (rel abundance) 300 ((M+H)⁺, 50%).

NH₃⁺ Cl⁻

io Step 3, 5-tert-Butyl thiopheneammonium Chloride: A solution of 3-(tert-butoxycarbonylarnino) tert-butyl thiophenecarboxylic acid (3.0 g, 0.010 mol) in dioxane (20 mL) was treated with an HO solution (4.0 M in dioxane, 12.5 mL, 0.050 mol, 5.0 equiv), and the resulting mixture was heated at 80 °C for 2 h. The resulting cloudy solution was allowed to cool to room temp forming some precipitate. The slurry was diluted with EtOAc (50 mL) and cooled to -20 °C. The resulting solids were collected and dried overnight under reduced pressure to give the desired salt as an off-white solid (1.72 g, 90%): ¹H-NMR (DMSO-d₆) δ 1.31 (s, 9H), 6.84 (d, J=1.48 Hz, 1H), 7.31 (d, J=1.47 Hz, 1H), 10.27 (br s, 3H).

2o A5. General Method for the Synthesis of BOC-Protected Pyrazoles

N

NH₂

O

5-Amino tert-butyl-]V-(tert-butoxycarbonyl)pyrazole: To a solution of 5-amino-3-tert-butylpyrazole (3.93 g, 28.2 mmol) in CH₂Cl₂ (140 mL) was added di-tert-butyl dicarbonate (6.22 g, 28.5 mmol) in one portion. The resulting solution was stirred at room temp. for 13 h, then diluted with EtOAc (500 mL). The organic layer was washed with water (2 x 300 mL), dried (MgSO₄) and concentrated under reduced pressure. The solid residue was triturated (100 mL hexane) to give the desired carbamate (6.26 g, 92%): mp 63-64 °C; TLC R_f (5% acetone/95% CH₂Cl₂); ¹H-NMR (DMSO-d₆) δ 1.15 (s, 9H), 1.54 (s, 9H), 5.22 (s, 1H), 6.11 (s, 2H); FAB-MS m/z ((M+H)).

A6. General Method for the Synthesis of 2-Aminothiadiazaoles

S

N

%N::kNH₂

2-Amino (1-(1-ethyl)propyl)thiadiazine: To concentrated sulfuric acid (9.1 mL) was slowly added 2-ethylbutyric acid (10.0 g, 86-mmol, 1.2 equiv). To this mixture was slowly added thiosemicarbazide (6.56 g, 72 mmol, 1 equiv). The reaction mixture was heated at 85 °C for 7 h, then cooled to room temperature, and treated with a concentrated NH₄OH solution until basic. The resulting solids were filtered to afford 2-amino (1-(1-ethyl)propyl)thiadiazine product was isolated via vacuum filtration as a beige solid (6.3 g, 51%): mp 155-158 °C; TLC (5% MeOH/ 95% CHCl₃) R_f 0.14; ¹H-NMR (DMSO-d₆) δ 0.80 (t, J=7.35 Hz, 6H), 1.60 (in, 2H), 1.71 (in, 2H), 2.74 (m, 1H), 7.00 (br s, 2H); HPLC ES-MS m/z 172 ((M+H)+).

2o A7, General Method for the Synthesis of 2-Aminooxadiazoles

O

N' NH₂

H

Step 1. Isobutyric Hydrazide: A solution of methyl isobutyrate (10.0 g) and hydrazine (2.76 g) in MeOH (500 mL) was heated at the reflux. temperature over night then stirred at 60 °C for 2 weeks. The resulting mixture was cooled to room temperature and concentrated under reduced pressure to afford isobutyric hydrazide as a yellow oil (1.0 g, 10%), which was used inb the next step without further purification.

N

%N::kNH₂

Step 2. 2-Amino isopropyl oxadiazole: To a mixture of isobutyric hydrazide (0.093 g), KHCO₃ (0.102 g), and water (1 mL) in dioxane (1 mL) at room temperature was added cyanogen bromide (0.10 g). The resulting mixture was heated at the reflux temperature for 5 h, and stirred at room temperature for 2 d, then treated with C11202 (5 mL). The organic layer was washed with water (2 x 10 mL), dried (MgSO₄) and concentrated under reduced pressure to afford 2-amino isopropyl oxadiazole as a white solid: BPLC ES-MS m/z 128 ((M+H)⁺).

io A8. General Method for the Synthesis of 2-Aminooxazoles

O

OH

Step 1. 3,3-Dimethyl-1-hydroxy butanone: A neat sample of 1-bromo-3,3-dimethyl butanone (33.3 g) at 0 °C was treated with a 1N NaOH solution, then was stirred for 1 h. The resulting mixture was extracted with EtOAc (5 x 100 mL). The combined organics were dried (Na₂SO₄) and concentrated under reduced pressure to give 3,3-dimethyl-1-hydroxy butanone (19 g, 100%), which was used inb the next step without further purification.

N

NH₂

Step 2. 2-Amino-4-isopropyl-1,3-oxazole: To a solution of 3,3-dimethyl-1-hydroxy butanone (4.0 g) and cyanamide (50% w/w, 2.86 g) in TBF (10 mL) was added a 1N NaOAc solution (8 mL), followed by tetra-n-butylammonium hydroxide (0.4 M, 3.6 mL), then a 1N NaOH solution (1.45 mL). The resulting mixture was stirred at room temperature for 2 d. The resulting organic layer was separated, washed with water (3 x 25 mL), and the aqueous layer was extracted with Et₂O (3 x 25 mL). The combined organic layers were treated with a 1N NaOH solution until basic, then extracted with C11202 (3 x 25 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to afford 2-Amino isopropyl-1,3-oxazole (1.94 g, 41 %): HPLC ES-MS m/z 141 ((M+H)⁺).

A9. Method for the Synthesis of Substituted aminotetrazoles

/N'N

N1]'

Nj-'],NH₂

To a solution of 5-aminotetrazole (5 g), NaOH (2.04 g) and water (25 mL) in

EtOH

(15 mL) at the reflux temperature was added 2-bromopropane (5.9 g). The resulting mixture was heated at the reflux temperature for 6 d, then cooled to room temperature, and concentrated under reduced pressure. The resulting aqueous mixture was washed with CH_2Cl_2 (3 x 25 mL), then concentrated under reduced pressure with the aid of a rotary evaporator to afford a mixture of 1- and 2-isopropyl aminotetrazole (50%), which was used without further purification: HPLC ES-MS m/z 128 ((M+H)+).

B, General Methods for Synthesis of Substituted Anilines

B1. General Method for Substituted Aniline Formation via Hydrogenation of a Nitroarene

N

$\text{H}_2\text{NJD}']]\text{O}]\text{It}$

4-(4-Pyridinylmethyl)aniline: To a solution of 4-(4-nitrobenzyl)pyridine (7.0 g, 32.68 mmol) in EtOH (200 mL) was added 10% Pd/C (0.7 g) and the resulting slurry was shaken under a H_2 atmosphere (50 psi) using a Parr shaker. After 1 h, TLC and ^1H -NMR of an aliquot indicated complete reaction. The mixture was filtered through a short pad of Celite. The filtrate was concentrated in vacuo to afford a white solid (5.4 g, 90%): ^1H -NMR ($\text{DMSO}-d_6$) δ 3.74 (s, 2H), 4.91 (br s, 2H), 6.48 (d, $J=8.46$ Hz, 2H), 6.86 (d, $J=8.09$ Hz, 2H), 7.16 (d, $J=5.88$ Hz, 2H), 8.40 (d, $J=5.88$ Hz, 2H); EI-MS m/z 184 (M). This material was used in urea formation reactions without further purification.

B2. General Method for Substituted Aniline Formation via Dissolving Metal Reduction of a Nitroarene

4-(2-Pyridinylthio)aniline: To a solution of 4-(2-pyridinylthio)-1-nitrobenzene

(Menai ST 3355A; 0.220 g, 0.95 mmol) and H_2O (0.5 mL) in AcOH (5 mL) was added iron powder (0.317 g, 5.68 mmol) and the resulting slurry stirred for 16 h at room temp. The reaction mixture was diluted with EtOAc (75 mL) and H_2O (50 mL), basified to pH 10 by adding solid K_2CO_3 in portions (Caution: foaming). The

organic layer was washed with a saturated NaCl solution, dried (MgSO_4), concentrated in vacuo. The residual solid was purified by NTLC (30% EtOAc/70% hexane) to give the desired product as a thick oil (0.135 g, 70%): TLC (30% EtOAc/70% hexanes) R_f 0

B3a, General Method for Substituted Aniline Formation via Nitroarene

Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction

02N OMe

Step 1. 1-Methoxy-4-(4-nitrophenoxy)benzene: To a suspension of NaH (95%, 1.50 g, 59 mmol) in DMSO (100 mL) at room temp. was added dropwise a solution of

4-methoxyphenol (7.39 g, 59 mmol) in DMF (50 mL). The reaction was stirred 1 h,

then a solution of 1-fluoro-4-nitrobenzene (7.0 g, 49 mmol) in DMF (50 mL) was

added dropwise to form a dark green solution. The reaction was heated at 95 °C overnight, then cooled to room temp., quenched with H₂O, and concentrated in vacuo.

The residue was partitioned between EtOAc (200 mL) and H₂O (200 mL). The organic layer was sequentially washed with H₂O (2 x 200 mL), a saturated NaHCO₃ solution (200 mL), and a saturated NaCl solution (200 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was triturated (Et₂O/hexane) to afford 1-methoxy (4-nitrophenoxy)benzene (12.2 g, 100%): ¹H-NMR (CDCl₃) δ 3.83 (s, 3H), 6.70 (m, 6H), 8.18 (d, J=9.2 Hz, 2H); EI-MS m/z 245 (M⁺).

H₂N We

Step 2. 4-(4-Methoxyphenoxy)aniline: To a solution of 1-methoxy (4-

nitrophenoxy)benzene (12.0 g, 49 mmol) in EtOAc (250 mL) was added 5% Pt/C (1.5 g) and the resulting slurry was shaken under a H₂ atmosphere (50 psi) for 18 h.

The reaction mixture was filtered through a pad of Celite with the aid of EtOAc and concentrated in vacuo to give an oil which slowly solidified (10.6 g, 100%): ¹H-NMR (CDCl₃) δ 3.54 (br s, 2H), 3.78 (s, 3H), 6.65 (d, J=8.8 Hz, 2H), 6.92 (m, 6H); EI-MS m/z 215 (M).

B3b. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction
CF₃

O₂N

Step 1. 3-(Trifluoromethyl) (4-pyridinylthio)nitrobenzene: A solution of 4-mercaptopyridine (2.8 g, 24 mmol), 2-fluoro nitrobenzotrifluoride (5 g, 23.5 mmol), and potassium carbonate (6.1 g, 44.3 mmol) in anhydrous DMF (80 mL) was stirred at room temperature and under argon overnight. TLC showed complete reaction. The mixture was diluted with Et₂O (100 mL) and water (100 mL) and the aqueous layer was back-extracted with Et₂O (2 x 100 mL). The organic layers were washed with a saturated NaCl solution (100 mL), dried (MgSO₄), and concentrated under reduced pressure. The solid residue was triturated with Et₂O to afford the desired product as a tan solid (3.8 g, 54%): TLC (30% EtOAc/70% hexane) R_f 0.06; ¹H-NMR (DMSO-d₆) δ 7.33 (dd, J=1.2, 4.2 Hz, 2H), 7.78 (d, J=8.7 Hz, 1H), 8.46 (dd, J=2.4, 8.7 Hz, 1H), 8.56 (m, 3H).

CF₃

ss']

H₂N N

Step 2. 3-(Trifluoromethyl)4-(4-pyridinylthio)aniline: A slurry of 3-trifluoromethyl (4-pyridinylthio)nitrobenzene (3.8 g, 12.7 mmol), iron powder (4.0

g, 71.6 mmol), acetic acid (100 mL), and water (1 mL) were stirred at room temp. for

h. The mixture was diluted with Et₂O (100 mL) and water (100 mL). The aqueous

phase was adjusted to pH 4 with a 4 N NaOH solution. The combined organic layers

were washed with a saturated NaCl solution (100 mL), dried (MgSO₄), and concentrated under reduced pressure. The residue was filtered through a pad of silica

(gradient from 50% EtOAc/50% hexane to 60% EtOAc/40% hexane) to afford the desired product (3.3 g): TLC (50% EtOAc/50% hexane) R_f 0.10; ¹H-NMR (DMSO-
Q 8 6.21 (s, 2H), 6 6.87 (m, 3H), 7.10 (d, J=2.4 Hz, 1H), 7.39 (d, J=8.4 Hz, 1H),

8.29 (d, J=6.3 Hz, 2H).

io We. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction
SY11 S

02N N

Step 1. 4-(2-(4-Phenyl)thiazolyl)thio-1-nitrobenzene: A solution of 2-mercapto

phenylthiazole (4.0 g, 20.7 mmol) in DMF (40 mL) was treated with 1-fluoro 1 5 nitrobenzene (2.3 mL, 21.7 mmol) followed by K₂CO₃ (3.18 g, 23 mmol), and the

mixture was heated at approximately 65 °C overnight. The reaction mixture was then

diluted with EtOAc (100 mL), sequentially washed with water (100 mL) and a saturated NaCl solution (100 mL), dried (MgSO₄) and concentrated under reduced

pressure. The solid residue was triturated with a Et₂O/hexane solution to afford the

2o desired product (6.1 g): TLC (25% EtOAc/75% hexane) R_f 0.49; ¹H-NMR (CDCl₃) 8

7 7.47 (m, 3H), 7 7.63 (m, 3H), 7.90 (d, J=6.9 Hz, 2H), 8.19 (d, J=9.0 Hz, 2H).

SY1 S

H2N N

Step 2. 4-(2-(4-Phenyl)thiazolyl)thioaniline: 4-(2-(4-Phenyl)thiazolyl)thio-1-nitro-

benzene was reduced in a manner analogous to that used in the preparation of 3-

(trifluoromethyl) (4-pyridinylthio)aniline: TLC (25% EtOAc/75% hexane) R_f 0.18;

¹H-NMR (CDCl₃) 8 3.89 (br s, 2H), 6 6.77 (m, 2H), 7 7.53 (m, 6H), 7 7.89 (m, 2H).

B3d. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction
0 rj]

02NJ:]r

Step 1. 4-(6-Methyl pyridinyloxy)-1-nitrobenzene: To a solution of 5-hydroxy-2-methylpyridine (5.0 g, 45.8 mmol) and 1-fluoro nitrobenzene (6.5 g, 45.8 mmol)

in anhyd DNT (50 mL) was added K₂CO₃ (13.0 g, 91.6 mmol) in one portion. The mixture was heated at the reflux temp. with stirring for 18 h and then allowed to cool

to room temp. The resulting mixture was poured into water (200 mL) and extracted

with EtOAc (3 x 150 mL). The combined organics were sequentially washed with

water (3 x 100 mL) and a saturated NaCl solution (2 x 100 mL), dried (Na₂SO₄), and concentrated in vacuo to afford the desired product (8.7 g, 83%). The material was carried to the next step without further purification.

ON N
H₂NJ]r

Step 2. 4-(6-Methyl pyridinyloxy)aniline: A solution of 4-(6-methyl pyridinyloxy)-1-nitrobenzene (4.0 g, 17.3 mmol) in EtOAc (150 mL) was added to 10% Pd/C (0.500 g, 0.47 mmol) and the resulting mixture was placed under a H₂ atmosphere (balloon) and was allowed to stir for 18 h at room temp. The mixture was then filtered through a pad of Celite and concentrated in vacuo to afford the desired product as a tan solid (3.2 g, 92%): EI-MS m/z 200 (m).

We. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction

0 OMe

02N OMe

Step 1. 4-(3,4-Dimethoxyphenoxy)-1-nitrobenzene: To a solution of 3,4-dimethoxyphenol (1.0 g, 6.4 mmol) and 1-fluoro nitrobenzene (700 μ L, 6.4 mmol) in anhydrous DMF (20 mL) was added K₂CO₃ (1.8 g, 12.9 mmol) in one portion. The mixture was heated at the reflux temp with stirring for 18 h and then allowed to cool to room temp. The mixture was then poured into water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organics were sequentially washed with water (3

We

H₂N We

Step 2. 4-(3,4-Dimethoxyphenoxy)aniline: A solution of 4-(3,4-dimethoxyphenoxy)-1-nitrobenzene (0.8 g, 3.2 mmol) in EtOAc (50 mL) was added to 10% Pd/C (0.100 g) and the resulting mixture was placed under a H₂ atmosphere (balloon) and was allowed to stir for 18 h at room temp. The mixture was then filtered through a pad of Celite and concentrated in vacuo to afford the desired product as a white solid (0.6 g, 75%): EI-MS m/z 245 (M).

BU General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction

N

02N

Step 1, 3-(3-Pyridinyloxy)-1-nitrobenzene: To a solution of 3-hydroxypyridine (2.8 g, 29.0 mmol), 1-bromo nitrobenzene (5.9 g, 29.0 mmol) and copper(I) bromide (5.0 g, 34.8 mmol) in anhydrous DMF (50 mL) was added K₂CO₃ (8.0 g, 58.1 mmol) in one portion. The resulting mixture was heated at the reflux temp. with stirring for 18 h and then allowed to cool to room temp. The mixture was then poured into water (200 mL) and extracted with EtOAc (3 x 150 mL). The combined organics were sequentially washed with water (3 x 100 mL) and a saturated NaCl solution (2 x 100 mL), dried (Na₂SO₄), and concentrated in vacuo. The resulting oil was

purified
by flash chromatography (30% EtOAc/70% hexane) to afford the desired product
(2.0
g, 32 %). This material was used in the next step without further
purification.

N

H2N OfIJI

Step 2. 3-(3-Pyridinyloxy)aniline: A solution of 3-(3-pyridinyloxy)-1-nitrobenzene (2.0 & 9.2 mmol) in EtOAc (100 mL) was added to 10% Pd/C (0.200 g)

and the resulting mixture was placed under a H₂ atmosphere (balloon) and was allowed to stir for 18 h at room temp. The mixture was then filtered through a pad of

B3g. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction

N

02N

Step 1. 3-(5-Methyl pyridinyloxy)-1-nitrobenzene: To a solution of 3-hydroxy-5-methylpyridine (5.0 g, 45.8 mmol), 1-bromo nitrobenzene (12.0 g, 59.6 mmol) and copper(I) iodide (10.0 g, 73.3 mmol) in anhyd DMF (50 mL) was added K₂CO₃ (13.0 g, 91.6 mmol) in one portion. The mixture was heated at the reflux temp. with

stirring for 18 h and then allowed to cool to room temp. The mixture was then poured

into water (200 mL) and extracted with EtOAc (3 x 150 mL). The combined organics

were sequentially washed with water (3 x 100 mL) and a saturated NaCl solution (2 x

100 mL), dried (Na₂SO₄), and concentrated in vacuo. The resulting oil was purified

by flash chromatography (30% EtOAc/70% hexane) to afford the desired product (1.2

g, 13%).

N

H2N

Step 2. 3-(5-Methyl pyridinyloxy)-1-nitrobenzene: A solution of 3-(5-methyl pyridinyloxy)-1-nitrobenzene (1.2 g, 5.2 mmol) in EtOAc (50 mL) was added to 10%

Pd/C (0.100 g) and the resulting mixture was placed under a H₂ atmosphere (balloon)

and was allowed to stir for 18 h at room temp. The mixture was then filtered through

a pad of Celite and concentrated in vacuo to afford the desired product as a red oil

(0.9 g, 86%): CI-MS m/z 201 ((M+H)⁺).

B3h, General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction

0

IC I

02N

Step 1. 5-Nitro (4-methylphenoxy)pyridine: To a solution of 2-chloro nitropyridine (6.34 g, 40 mmol) in DW (200 mL) were added 4-methylphenol (5.4

1.942 g, 40 mmol) and K₂CO₃ (10.0 g, 80 mmol) in one portion. The mixture was heated at the reflux temp. with stirring for 18 h and then allowed to cool to room temp. The mixture was then poured

into water (200 mL) and extracted with EtOAc (3 x 150 mL). The combined organics

were sequentially washed with water (3 x 100 mL) and a saturated NaCl solution (2 x

poglu-tr jo uolinjos r oL :au;azuagoillu-l-(oiqllAuaigj,-E)- I dals
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 uollanpan Sq pamolloa luoi njjjsqnS 3i viaoiV ai ilqdoal3nbj q3noiqlL uoi
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 OZ
 'zH 60*8=F'P) 610L '(HI 'zH Z8]8=f 4P) VO*L '(HZ 'zH 917*8=,r 6P) 86*9 IHE
 's) 9Z*Z
 2 (9P-OSWG) IdM-Hj tZt7eo -f-d (nipa lad %og/oVoig %og) DrjL !(oop) Do 0 1
 Z-80Z
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 aq,L *(2 09*0) Dipcl %01 ql!m polvail uzql uogm qltA poSind srm (qw 061)
 OV01a
 u! (qm 01) H01H PUB (bg I '10ulEu OE T V6-9) Ou'PLL]d(XxouoqdlSqlc)w-t)-Z-
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 -g uoilnlos V :apjiojq-3oapSq!(j auipliSd(Sxouaqdlgqlaui-t)-Z-ouimV-S -Z dals
 ol
 +WH .10
 -10%) +H
 '(, (H+W)) I CZ (00uuPungv 101) z/w SW-EIVJ !(HI 'zH 96'Z=r'P) 66*8 IHI 'zH
 Z808
 'tp6]Z=r 4PP) 89*8 '(HZ 'zH 60&8=r'p) t?Z*L '(HI 'zH OZ06=r'P) 6I&L 4(HZ'zH
 9t7]8=r
 'P) 80*L 'WE 4s) IE'Z 2 OP-OSIARD UM-H, t6L6O -d (.ioqlo lad %oL/oVojq %OC)
 Drjj!D,Z8-08dui :(%gL'Sgo[L)IonpoidpaiisopgqlgAISOI(lMgZ).ioqloladpuu g
 Nm 9Z) -1QTuM'(quI 9Z) u0ljnl0s H09M X Iuqj!m polqwm Alluilonbas pug polmdos
 oiam spljos oqj pue 'q I ioj pom s srm 3jmxui si
 qjL -ojuj!diooid u 0jriou02? ol (qtu
 009) jolum qwA polvan sum omilxitu Sutllnsoi oqj -dtuol tuooi it! jq2RUQA0
 POMIS
 SUM QnljXlui QqL '(AMBo g*1 41OUIM 09 T 8Z*8) EODZ'X PtM (AlnBo 5Z'l 41OUIEU
 Og
 0809Z/86Sfl/JL3d I II ZC/66 OM
 S
]] CS
 H2NJ::]
 io Step 2, 4-(3-Thienylthio)aniline: 4-(3-Thienylthio)-1-nitrobenzene was
 reduced to
 the aniline in a manner analogous to that described in Method B 1.

B3j. General Method for Substituted Aniline Formation via Nitroarene
 Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction

O

N

H2N N

4-(5-Pyrimininyloxy)aniline- , 4-Aminophenol (1.0 g, 9.2 mmol) was dissolved
 in

DMF (20 mL) then 5-bromopyrimidine (1.46 g, 9.2 mmol) and K2CO3 (1.99 g, 13.7
 mmol) were added. The mixture was heated to 100 °C for 18 h and at 130 °C for

48 h

2o at which GC-MS analysis indicated some remaining starting material. The reaction mixture was cooled to room temp. and diluted with water (50 mL). The resulting solution was extracted with EtOAc (100 mL). The organic layer was washed with a saturated NaCl solution (2 x 50 mL), dried (MgSO₄), and concentrated in vacuo. The residual solids were purified by MPLC (50% EtOAc/50% hexanes) to give the desired amine (0.650 g, 38%).

Wk. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction
Br We

N

CZ&9) SI-01SA10 M0110X P-I0JJV 01 (QuRxQq/3v0ja POZI ISAJO oc

. it,

swA ljo utAojq Irnp!soj axU -omssaid poonpaiapun poir.4mmoo ptm (VOSS pau YD . p

sutA -IOAE1 Oung-IO QU '(1m 9L x Z) OV019 TPA PO13V-4x0 PuR (qm 9Z) -MIUM lp!M

POI 4 UOqj 4jqSjEUOAO Do 96 01 POTBOXI SWA O'Mxlum 1101 OvO-I Oq1 -OSXILL]S EIA POPPE

SwA QOunu 8z 6qm C) ouozuaqo4juoionU-t7 cq I joj -dtuol uiioi ju mis ol pomoll-B

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P.

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x Z) Ozlg TPA PO10V-4xz 110111 u0'jn10s IDH N1 oql!m pazil'unnou summkol snoonbv

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xnUoi oqj ol poluoig uoql pue unu OCioj -dmaj Luooi ol poumm srm ainixitu uoil 00.1

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90*L) olvioq jj(qjouijjjL 917 -10J Do 8L- 1-8 -Ills 01 POMOHE sum oimxnu Sul Insai

.1

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-u uE POPPE sTM Do 8L- It! (qm 9LO MI III (1OuRu 6-L17 'S 6-8)

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 g
 Qq6L *(qm 001 X Z) OV01a tp!M POj3V-1lX0 PUR (qtU 0g).IajVtA ql!M POIVO.4 SUM
 OJMXIT.U
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 P01-80S r UR
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 g-g) ou!p!jAdouioiq!p-g'Z JO om,4xitu V :auipl!.iSdSxoqjatu-Z-omo.1jj-S el
 dajs

0809Z/86Sfl/13d Os; I II U/66 OM

B4a. General Method for Substituted Aniline Synthesis via Nucleophilic Aromatic Substitution using a Halopyridine

] N

H2NJasl)]

3-(4-Pyridinylthio)aniline: To a solution of 3-aminothiophenol (3.8 mL, 34 mmol)

I 0 in anh DMF (90mL) was added 4-chloropyridine hydrochloride (5.4 g, 35.6 mmol)

followed by K₂CO₃ (16.7 g, 121 mmol). The reaction mixture was stirred at room

temp. for 1.5 h, then diluted with EtOAc (100 mL) and water (100mL). The aqueous

layer was back-extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with a saturated NaCl solution (100 mL), dried (MgSO₄), and concentrated under reduced pressure. The residue was filtered through a pad of silica

(gradient from 50% EtOAc/50% hexane to 70% EtOAc/30% hexane) and the resulting material was triturated with a Et₂O/hexane solution to afford the desired

product (4.6 g, 66%): TLC (100 % ethyl acetate) R_f 0.29; ¹H-NMR (DMSO-d₆) δ

5.41 (s, 2H), 6.674 (m, 3H), 7.01 (d, J=4.8, 2H), 7.14 (t, J=7.8 Hz, 1H), 8.32 (d, J=4.8, 2o 2H).

B4b. General Method for Substituted Aniline Synthesis via Nucleophilic Aromatic Substitution using a Halopyridine

H2N

4-(2-Methyl pyridinyloxy)aniline: To a solution of 4-aminophenol (3.6 g, 32.8 mmol) and 4-chloropicoline (5.0 g, 39.3 mmol) in anh DMPU (50 mL) was added potassium tert-butoxide (7.4 g, 65.6 mmol) in one portion. The reaction mixture was

heated at 100 °C with stirring for 18 h, then was allowed to cool to room temp. The

resulting mixture was poured into water (200 mL) and extracted with EtOAc (3 x 150

B4c. General Method for Substituted Aniline Synthesis via Nucleophilic Aromatic Substitution using a Halopyridine

Me

02N--O-ri

io Step 1, Methyl(4-nitrophenyl) pyridylamine: To a suspension of N-methyl nitroaniline (2.0 g, 13.2 mmol) and K₂CO₃ (7.2 g, 52.2 mmol) in DMPU (30mL) was

added 4-chloropyridine hydrochloride (2.36 g, 15.77 mmol). The reaction

B5. General Method of Substituted Aniline Synthesis via Phenol Alkylation Followed by Reduction of a Nitroarene

3/29/04

0 NzH 91

S

6 (HZ'zHL*8=r'P)15*L '(HZ

'zH6=r'P)LI*L 6 (HZ'zHL'8=F'P)80*L '(HZ6zH9*9=rgi)io,tr '(HZ4Tu)0L*1 '(HZ

'zH5*L=r'xoqdd,u)Zt7*j '(HE4zHg'L=,r4l)Z6*02(9P-OSW(I)UWM-H, !9L f-d

(OlluxQ11 %08/3V019 %OZ) DU :(%L9 'S tpZ-1) p!los molloA le sT lonpoid otp

OA12 01

(ouexo,q %05/oVoig %og ol ouuxoq %08/oVola %OZ uiog luo!pua) AqduBojouioxq-3
ol

lo2 uoi is Aq poglmd s-em q-3i

.qm '1!0 M011OX =13 V OA12 ol Qmssoid poonpai

.iopun poiriluumoo pu-c 'QoSSW) pou

. p I(qw 00j7 x Z) nim pm poiqrsm wom

someRio poq!qtuo3 oql -(qw oog x Z) ozig ippA polouilxo sum ojmxiu Suilinsai
oiql

-(qW 0017) -10IRM JO UOT Ippi! oqj Aq poqouonb sum uoql 4-dwol tuooiq 9

peuoij!pptv

uu paulls sTtA uoi orai oqL -poppr wom (lounu trEE-0 Tua El) Hum -pug (ATnbQ
9

go-o 4lounu CoCoo 4qm 5EO,o Tui 9g) ouulngopoi Iruoi!ppu puu Ilouoqd pajoranm

Jo omosaid zqj pol-em DqL otup gou

.4m ju q 81 -ioj *dTuo! uiioi ju pom s sum

.Pui

UOI 3-00J Oqj, 'Do 0 1-0 UTT.U 51 lQAO osimdojp poppv sum, (qw OZ) jW(I quo
ui (lounu

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uoilnIOAQ

0809V86Sfl/13d I II U/66 OM

saturated NaHCO₃ solution (100 mL), water (100 mL) and a saturated NaCl
solution

(50 mL), dried (MgSO₄), and concentrated under reduced pressure. The
resulting

white solid was purified by silica gel chromatography (gradient from 33%
EtOAc/67% hexane to 50% EtOAc/50% hexane) to afford the desired product as a
white solid (2.09 g, 46%): TLC (50% EtOAc/50% hexane) R_f 0.45; ¹H-NMR

(DMSO-d₆) 5 1.43 (s, 9H), 3.63 (s, 2H), 4.85 (br s, 2H), 6.44 (d, J=8.4 Hz,
2H),

6.80 (d, J=8.1 Hz, 2H), 7.00 (d, J=8.4 Hz, 2H), 7.28 (d, J=8.1 Hz, 2H), 9.18

(br s,

1H); FAB-MS m/z 298 (M+).

io B7, General Method for the Synthesis of Aryl Amines via Electrophilic
Nitration Followed by Reduction

N

02NJO]]

Step 1. 3-(4-Nitrobenzyl)pyridine: A solution of 3-benzylpyridine (4.0 g,
23.6 mmol) and 70% nitric acid (30 mL) was heated overnight at 50 °C. The
resulting

mixture was allowed to cool to room temp. then poured into ice water (350
mL). The

aqueous mixture then made basic with a 1N NaOH solution, then extracted with
Et₂O

(4 x 100 mL). The combined extracts were sequentially washed with water (3 x
100

mL) and a saturated NaCl solution (2 x 100 mL), dried (Na₂SO₄), and
concentrated in

vacuo. The residual oil was purified by MPLC (silica gel; 50 % EtOAc/50%
hexane)

then recrystallization (EtOAc/hexane) to afford the desired product (1.0 g,
22%): GC-

MS mlz 214 (M).

N

H 2 N

Step 2. 3-(4-Pyridinyl)methylaniline: 3-(4-Nitrobenzyl)pyridine was reduced to the aniline in a manner analogous to that described in Method B 1.

B8. General Method for Synthesis of Aryl Amines via Substitution with Nitrobenzyl Halides Followed by Reduction

NL

02NJ::r N

Step 1. 4-(1-Imidazolylmethyl)-1-nitrobenzene: To a solution of imidazole (0.5 g, 7.3 mmol) and 4-nitrobenzyl bromide (1.6 g, 7.3 mmol) in anhydrous acetonitrile (30 mL) was added K₂CO₃ (1.0 g, 7.3 mmol). The resulting mixture was stirred at room temp. for 18 h and then poured into water (200 mL) and the resulting aqueous solution was extracted with EtOAc (3 x 50 mL). The combined organic layers were sequentially washed with water (2 x 50 mL) and a saturated NaCl solution (2 x 50 mL), dried (MgSO₄), and concentrated in vacuo. The residual oil was purified by MPLC (silica gel; 25% EtOAc/75% hexane) to afford the desired product (1.0 g, 91 %): EI-MS mlz 203 (M).

H2NJ:::r N

Step 2. 4-(1-Imidazolylmethyl)aniline: 4-(1-Imidazolylmethyl)-1-nitrobenzene was reduced to the aniline in a manner analogous to that described in Method B2.

B9. Formation of Substituted Hydroxymethylanilines by Oxidation of Nitrobenzyl Compounds Followed by Reduction

OH

02N N

Step 1, 4-(1-Hydroxy-1-(4-pyridyl)methyl)-1-nitrobenzene: To a stirred solution of 3-(4-nitrobenzyl)pyridine (6.0 g, 28 mmol) in CH₂Cl₂ (90 mL) was added m-CPBA (5.80 g, 33.6 mmol) at 10 °C, and the mixture was stirred at room temp. overnight.

The reaction mixture was successively washed with a 10% NaHSO₃ solution (50 mL), a saturated K₂CO₃ solution (50 mL) and a saturated NaCl solution (50 mL), dried (MgSO₄) and concentrated under reduced pressure. The resulting yellow solid (2.68 g) was dissolved in anhydrous acetic anhydride (30 mL) and heated at the reflux temperature overnight. The mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (25 mL) and treated with a 20% aqueous NH₃ solution (30 mL).

The mixture was stirred at room temp. for 1 h, then was concentrated under reduced pressure. The residue was poured into a mixture of water (50 mL) and CH₂Cl₂ (50

mL). The organic layer was dried (MgSO₄), concentrated under reduced pressure, and purified by column chromatography (80% EtOAc/ 20% hexane) to afford the desired product as a white solid. (0.53 g, 8%): mp 110-118 °C; TLC (80% EtOAc/20% hexane) R_f 0.12; FAB-MS m/z 367 ((M+H)⁺) 100%.

OH

H₂N N

Step 2. 4-(1-Hydroxy-1-(4-pyridyl)methylaniline: 4-(1-Hydroxy-1-(4-pyridyl)-1-methyl-1-nitrobenzene was reduced to the aniline in a manner analogous to that described in Method B3d, Step2.

B10. Formation of 2-(N-methylcarbamoyl)pyridines via the Menisci reaction

O

CI NH₂

N

Step 1, 2-(N-methylcarbamoyl) chloropyridine. (Caution: this is a highly hazardous, potentially explosive reaction.) To a solution of 4-chloropyridine (10.0 g) in N-methylformamide (250 mL) under argon at ambient temp was added conc.

H₂SO₄ (3.55 mL) (exotherm). To this was added H₂O₂ (17 mL, 30% wt in H₂O) followed by FeSO₄·7H₂O (0.55 g) to produce an exotherm. The reaction was stirred in the dark at ambient temp for 1h then was heated slowly over 4 h at 45 °C. When

bubbling subsided, the reaction was heated at 60 °C for 16 h. The opaque brown solution was diluted with H₂O (700 mL) followed by a 10% NaOH solution (250 mL). The aqueous mixture was extracted with EtOAc (3 x 500 mL) and the organic

layers were washed separately with a saturated NaCl solution (3 x 150 mL).

The

combined organics were dried (MgSO₄) and filtered through a pad of silica gel eluting

with EtOAc. The solvent was removed in vacuo and the brown residue was purified

by silica gel chromatography (gradient from 50% EtOAc / 50% hexane to 80% EtOAc / 20% hexane). The resulting yellow oil crystallized at 0 °C over 72 h to give

2-(N-methylcarbamoyl) chloropyridine in yield (0.61 g, 5.3%): TLC (50% EtOAc/50% hexane) R_f 0.50; MS; ¹H NMR (CDCl₃): δ 8.44 (d, 1 H, J = 5.1 Hz, CHN), 8.21 (s, 1H, CHCO), 7.96 (b s, 1H, NH), 7.43 (dd, 1H, J = 2.4, 5.4 Hz, ClCHN), 3.04 (d, 3H, J = 5.1 Hz, methyl); CI-MS m/z 171 ((M+H)⁺).

B11. General method for the Synthesis of (o-Sulfonylphenyl) Anilines

O

Me

'S,

O₂N

O] O

Step 1. 4-(4-Methylsulfonylphenoxy)-1-nitrobenzene: To a solution of 4-(4-methylthiophenoxy)-1-nitrobenzene (2 g, 7.66 mmol) in CH₂Cl₂ (75 mL) at 0 °C was

slowly added mCPBA (57-86%, 4 g), and the reaction mixture was stirred at room

temperature for 5 h. The reaction mixture was treated with a 1 N NaOH solution (25

mL). The organic layer was sequentially washed with a 1N NaOH solution (25 mL),

water (25 mL) and a saturated NaCl solution (25 mL), dried (MgSO₄), and concentrated under reduced pressure to give 4-(4-methylsulfonylphenoxy)-1-nitrobenzene as a solid (2.1 g).

Step 2. 4-(4-Methylsulfonylphenoxy)-1-aniline: 4-(4-Methylsulfonylphenoxy)-1-nitrobenzene was reduced to the aniline in a manner analogous to that described in Method 133d, step 2.

B12. General Method for Synthesis of (o-Alkoxy-o)-carboxyphenyl Anilines

0

0 Ome

02NJcr OMe

Step 1. 4-(3-Methoxycarbonyl-4-methoxyphenoxy)-1-nitrobenzene: To a solution of 4-(3-carboxy-4-hydroxyphenoxy)-1-nitrobenzene (prepared in a manner analogous to that described in Method B3a, step 1, 12 mmol) in acetone (50 mL) was added

K₂CO₃ (5 g) and diisopropyl sulfate (3.5 mL). The resulting mixture was heated

at the reflux temperature overnight, then cooled to room temperature and filtered

through a pad of Celite. The resulting solution was concentrated under reduced

pressure, absorbed onto silica gel, and purified by column chromatography

(50% EtOAc / 50% hexane) to give 4-(3-methoxycarbonyl-4-methoxyphenoxy)-1-nitrobenzene as a yellow powder (3 g): mp 115-118 °C.

0 OH

02NJ:|r OMe

Step 2. 4-(3-Carboxy-4-methoxyphenoxy)-1-nitrobenzene: A mixture of 4-(3-methoxycarbonyl-4-methoxyphenoxy)-1-nitrobenzene (1.2 g), KOH (0.33 g), and water (5 mL) in MeOH (45 mL) was stirred at room temperature overnight and then

heated at the reflux temperature for 4 h. The resulting mixture was cooled to room

temperature and concentrated under reduced pressure. The residue was dissolved in

water (50 mL), and the aqueous mixture was made acidic with a 1N HCl solution.

The resulting mixture was extracted with EtOAc (50 mL). The organic layer was dried (MgSO₄) and concentrated under reduced pressure to give 4-(3-carboxy-4-methoxyphenoxy)-1-nitrobenzene (1.04 g).

C. General Methods of Urea Formation

Cla. Reaction of a Heterocyclic Amine with an Isocyanate

0 0

N)] Nicr]]C

H H

N-(5-tert-Butyl thiophenyl)-N'-(4-phenoxyphenyl)urea: To a solution of 5-tert-butyl thiophene-ammonium chloride (prepared as described in Method A4b; 7.28 g,

46.9 mmol, 1.0 equiv) in anhydrous DMF (80 mL) was added 4-phenoxyphenyl isocyanate (8.92 g, 42.21 mmol, 0.9 equiv) in one portion. The resulting solution was stirred at

50-60 °C overnight, then diluted with EtOAc (300 mL). The resulting solution was

sequentially washed with H₂O (200 mL), a 1 N HCl solution (50 mL) and a saturated

NaCl solution (50 mL), dried (Na₂SO₄), and concentrated under reduced pressure.

The resulting off-white solid was recrystallized (EtOAc/hexane) to give a white solid (13.7 g, 88%), which was contaminated with approximately 5% of bis(4-phenoxyphenyl)urea. A portion of this material (4.67 g) was purified by Rash chromatography (9% EtOAc/27% CH₂O₂/64% cyclohexane) to afford the desired product as a white solid (3.17 g).

Clb, Reaction of a Heterocyclic Arnine with an Isocyanate

O

N

N)] N

H H

N-(3-tert-Butyl isoxazolyl)-N]-(4-phenoxyphenyl)urea: To a solution of 5-amino tert-butylisoxazole (8.93 g, 63.7 mmol, 1 eq.) in CH₂O₂ (60 mL) was added

4-phenyloxyphenyl isocyanate (15.47 g, 73.3 mmol, 1.15 eq.) dropwise. The mixture

was heated at the reflux temp. for 2 days, eventually adding additional CH₂O₂ (80

mL). The resulting mixture was poured into water (500 mL) and extracted with Et₂O

(3 x 200 mL). The organic layer was dried (MgSO₄) then concentrated under reduced

pressure. The residue was recrystallized (EtOAc) to give the desired product (15.7 g,

io 70%): mp 182-184 IC; TLC (5% acetone/95% acetone) R_f 0.27; ¹H-NMR

(DMSO-d₆)

8 1.23 (s, 9H), 6.02 (s, 1H), 6.97 (dd, J=0.2, 8.8 Hz, 2H), 6.93 (d, J=8.8 Hz, 2H), 7.08

(t, J=7.4 Hz, 1H), 7.34 (m, 2H), 7.45 (dd, J=2.2, 6.6 Hz, 2H), 8.80 (s, 1H), 10.04 (s,

1H); FAB-MS m/z (rel abundance) 352 ((M+H)⁺, 70%).

Clc. Reaction of a Heterocyclic Arnine with an Isocyanate

O O

N)] N

H H

N-(3-tert-Butyl pyrazolyl)-N]-(4-(4-methylphenyl)oxyphenyl)urea: A solution of 5-amino tert-butylpyrazole (0.139 g, 1.0 mmol, 1.0 equiv) and 4-(4-methylphenoxy)phenyl isocyanate (0.225 g, 1.0 mmol 1.0 equiv) in toluene (10 mL)

was heated at the reflux temp. overnight. The resulting mixture was cooled to room

temp and quenched with MeOH (a few mL). After stirring for 30 min, the mixture

was concentrated under reduced pressure. The residue was purified by prep. HPLC

(silica, 50% EtOAc/50% hexane) to give the desired product (0.121 g, 33%): mp 204

IC; TLC (5% acetone/95% CH₂O₂) R_f 0.92; ¹H-NMR (DMSO-d₆) 8 1.22 (s, 9H), 2.24 (s, 3H), 5.92 (s, 1H), 6.83 (d, J=8.4 Hz, 2H), 6.90 (d, J=8.8 Hz, 2H), 7.13 (d,

J=8.4 Hz, 2H), 7.40 (d, J=8.8 Hz, 2H), 8.85 (s, 1H), 9.20 (br s, 1H), 11.94 (br s, 1H);

EI-MS m/z 364 (M⁺).

CId. Reaction of a Heterocyclic Amine with an Isocyanate

0

N]A'N CI

H H CI

N-(5-tert-Butyl thienyl)-N]-(2,3-dichlorophenyl)urea: Pyridine (0.163 mL, 2.02

mmol) was added to a slurry of 5-tert-butylthiopheneammonium chloride (Method A4c; 0.30 g, 1.56 mmol) and 2,3-dichlorophenyl isocyanate (0.32 mL)- 2.02 mmol) in

CH₂Cl₂ (10 mL) to clarify the mixture and the resulting solution was stirred at room

temp. overnight. The reaction mixture was then concentrated under reduced pressure

and the residue was separated between EtOAc (15 mL) and water (15 mL). The organic layer was sequentially washed with a saturated NaHCO₃ solution (15 mL), a

1N HCl solution (15 mL) and a saturated NaCl solution (15 mL), dried (Na₂SO₄), and

concentrated under reduced pressure. A portion of the residue was by preparative

HPLC (C-18 column; 60% acetonitrile/40% water/0.05% TFA) to give the desired urea (0.180 g, 34%): mp 169-170 °C; TLC (20% EtOAc/80% hexane) R_f 0.57; ¹H.

NMR (DMSO-d₆) δ 1.31 (s, 9H), 6.79 (s, 1H), 7.03 (s, 1H), 7.33 (m, 2H), 8.16

(dd, J=1.84, 7.72 Hz, 1H), 8.35 (s, 1H), 9.60 (s, 1H); ¹³C-NMR (DMSO-d₆) δ 31.9

(3Q 34.09 103.4] 116.1] 119.3] 120.0] 123.4] 128.19 131.6] 135.62 138.1, 151.72 155.2;

FAB-MS m/z (rel abundance) 343 ((M+H)⁺, 83%) 345 ((M+H+2)⁺, 56%) 347 ((M+H+4)⁺, 12%).

Cle. Reaction of a Heterocyclic Amine with an Isocyanate

0 CI

N% K

N N CI

H H

N-(3-tert-Butyl pyrazolyl)-N]-(3,4-dichlorophenyl)urea: A solution of 5-amino-

3-tert-butyl-1H-pyrazole (Method A5; 0.150 g, 0.63 mmol) and

3,4-dichlorophenyl isocyanate (0.118 g, 0.63 mmol) were in toluene (3.1 mL) was

stirred at 55 °C for 2 d. The toluene was removed in vacuo and the solid was redissolved in a mixture of CH₂Cl₂ (3 mL) and TFA (1.5 mL). After 30 min, the solvent was removed in vacuo and the residue was taken up in EtOAc (10 mL). The

resulting mixture was sequentially washed with a saturated NaHCO₃ solution (10 mL)

and a NaCl solution (5 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue

was purified by flash chromatography (gradient from 40% EtOAc/ 60% hexane to 55% EtOAc/ 5% hexane) to give the desired product (0.102 g, 48%): mp 182-184 °C;

TLC (40% EtOAc/60% hexane) R_f 0.05, FAB-MS m/z 327 ((M+H)⁺).

C2a. Reaction of a Heterocyclic Amine with Phosgene to Form an Isocyanate, then Reaction with Substituted Aniline

N

0 N=C=O

Step 1. 3-tert-Butyl isoxazolyl Isocyanate: To a solution of phosgene (20% in

toluene, 1.13 mL, 2.18 mmol) in CH₂Cl₂ (20 mL) at 0 °C was added anhydrous pyridine (0.176 mL, 2.18 mmol), followed by 5-amino tert-butylisoxazole (0.305 g, 2.18 mmol). The resulting solution was allowed to warm to room temp. over 1 h, and then was concentrated under reduced pressure. The solid residue dried in vacuo for 0.5 h.

S-]n
N 0
N)]N
H H

Step 2. N-(3-tert-Butyl isoxazolyl)-N]-(4-(4-pyridinylthio)phenyl)urea: The crude 3-tert-butyl isoxazolyl isocyanate was suspended in anhydrous toluene (10 mL) and

4-(4-pyridinylthio)aniline (0.200 g, 0.989 mmol) was rapidly added. The suspension was stirred at 80 °C for 2 h then cooled to room temp. and diluted with an EtOAc/CH₂Cl₂ solution (4:1, 125 mL). The organic layer was washed with water (100 mL) and a saturated NaCl solution (50 mL), dried (MgSO₄), and concentrated

under reduced pressure. The resulting yellow oil was purified by column chromatography (silica gel, gradient from 2% MeOH/98% CH₂Cl₂ to 4% MeOH/96% CH₂Cl₂) to afford a foam, which was triturated (Et₂O/hexane) in combination with

sonication to give the product as a white powder (0.18 g, 49%): TLC (5% C₂b. Reaction of a Heterocyclic Amine with Phosgene to Form an Isocyanate Followed by Reaction with Substituted Aniline

N N=C=O

Step 1. 5-tert-Butyl isoxazolyl Isocyanate: To a solution of phosgene (148 mL, 1.93 M in toluene, 285 mmol) in anhydrous CH₂Cl₂ (1 L) was added 3-amino tert-butylisoxazole (10.0 g, 71 mmol) followed by pyridine (46 mL, 569 mmol). The mixture was allowed to warm to room temp and stirred overnight (ca. 16 h), then mixture was concentrated in vacuo. The residue was dissolved in anhydrous THF (350 mL) and stirred for 10 min. The orange precipitate (pyridinium hydrochloride) was removed and the isocyanate-containing filtrate (approximately 0.2 M in THF) was used as a stock solution: GC-MS (aliquot obtained prior to concentration) m/z 166

0
N N Nj:]r
H H

Step 2. N-(5-tert-Butyl isoxazolyl)-N]-(4-(4-pyridinylthio)phenyl)urea: To a solution of 5-tert-butyl isoxazolyl isocyanate (247 mL, 0.2 M in THF, 49.4 mmol)

was added 4-(4-pyridinylthio)aniline (5 g, 24.72 mmol), followed by THF (50 mL) then pyridine (4.0 mL, 49 mmol) to neutralize any residual acid. The mixture was

stirred overnight (ca. 18 h) at room temp. Then diluted with EtOAc, (300 mL). The organic layer was washed successively with a saturated NaCl solution (100 mL), a saturated NaHCO₃ solution (100 mL), and a saturated NaCl solution (100 mL), dried (MgSO₄), and concentrated in vacuo. The resulting material was purified by

MPLC

(2 x 300 g silica gel, 30 % EtOAc/70% hexane) to afford the desired product as a white solid (8.24 g, 90 %): mp 178-179 °C; ¹H-NMR (DMSO-d₆) δ 1.28 (s, 9H), 6.51

9,W) I gCoottebung

101 zlu1 SW-I9 !(HI 's Iq) 009ZI '(HI 's Iq) 5Z]6 '(HI 4s Iq) Z6*8 '(HZ 'zH 9Z*9=Ar'P)

EVS '(HZ 'zH Z*6=f 'P) Eg*L '(HZ 'zH Z8*8=f 'P) 0 1 *L '(HZ 6zH gZ49=r 6P) 88*9 '(HI Oz

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'(HZ 'zH E8*8=f 'P) Z9*L '(HZ 4zH Z8*8=r V) ZgeL '(HZ 'zH 9Z'9=f 6P) 9669 '(HI 4s)

0809V86Sfl/ldd C9 1 1 1 U/66 OM

-']]

N 0

N)] N

H H

N-(3-tert-Butyl-1-methyl pyrazolyl)-N]-(4-(4-pyridinyloxy)phenyl)urea: To a solution of 5-amino tert-butyl-1-methylpyrazole (189 g, 1.24 mol) in anh. CH₂O₂

(2.3 L) was added NN'-carbonyldiimidazole (214 g, 1.32 mol) in one portion. The

mixture was allowed to stir at ambient temperature for 5 h before adding 4-(4-

pyridinyloxy)aniline. The reaction mixture was heated to 36 °C for 16 h. The resulting mixture was cooled to room temp, diluted with EtOAc (2 L) and washed

lo with H₂O (8 L) and a saturated NaCl solution (4 L). The organic layer was dried

(Na₂SO₄) and concentrated in vacuo. The residue was purified by crystallization (44.4% EtOAc/44.4% Et₂O/11.2% hexane, 2.5 L) to afford the desired urea as a white solid (230 g, 51%): mp 149-152 °C; ¹H-NMR (DMSO-d₆) δ 1.18 (s, 9H), 3.57 (s, 3H), 6.02 (s, 1H), 6.85 (d, J=6.0 Hz, 2H), 7.08 (d, J=9.0 Hz, 2H), 7.52 (d, J=9.0 Hz, 2H), 8.40 (d, J=6.0 Hz, 2H), 8.46 (s, 1H), 8.97 (s, 1H); FAB-LSIMS m/z 366 ((M+H)).

C3b, Reaction of a Heterocyclic Amine with NN'-Carbonyldiimidazole Followed by Reaction with a Substituted Aniline

O S N

N N

H H

N-(3-tert-Butyl pyrazolyl)-N'-(3-(4-pyridinylthio)phenyl)urea: To a solution of

5-amino tert-butyl-1H-pyrazole (0.282 g, 1.18 mmol) in CH₂Cl₂ (1.2 mL) was added NN'-carbonyldiimidazole (0.200 g, 1.24 mmol) and the mixture was allowed to stir at room temp. for 1 day. 3-(4-pyridinylthio)aniline (0.239

g, 1.18 mmol) was added to the reaction solution in one aliquot and the resulting

mixture was allowed to stir at room temp. for 1 day. Then resulting solution was

treated with a 10% citric acid solution (2 mL) and was allowed to stir for 4 h. The

organic layer was extracted with EtOAc (3 x 15 mL), dried (MgSO₄), and concentrated in vacuo. The residue was diluted with CH₂Cl₂ (5 mL) and trifluoroacetic acid (2 mL) and the resulting solution was allowed to stir for 4 h. The

trifluoroacetic reaction mixture was made basic with a saturated NaHCO₃ solution,

then extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash chromatography (5% MeOH/95% CH₂Cl₂). The resulting brown solid was triturated with sonication (50% Et₂O/50% pet. ether) to give the desired urea (0.122 g, 28%).

mp >224 °C dec; TLC (5% MeOH/ 95% CHCl₃) R_f 0.067; ¹H-NMR (DMSO-d₆) δ 1.23 (s, 9H), 5.98 (s, 1H), 7.04 (drn, J=13.24 Hz, 2H), 7.19 (m, 1H), 7.47 (m, 2H), 7.82 (m, 1H), 8.36 (dm, J=15.44 Hz, 2H), 8.96 (br s, 1H), 9.32 (br s, 1H), 11.97 (br s, 1H); FAB-MS m/z (rel abundance) 368 QvI% 100%).

C4a. Reaction of Substituted Aniline with NN'-Carbonyldiimidazole Followed by Reaction with a Heterocyclic Amine

N N

O

N N

H H

N-(3-tert-Butyl-1-methyl pyrazolyl)-N'-(4-(4-pyridinylmethyl)phenyl)urea: To a solution of 4-(4-pyridinylmethyl)aniline (0.200 g, 1.08 mmol) in CH₂Cl₂ (10 mL)

was added NN'-carbonyldiimidazole (0.200 g, 1.23 mmol). The resulting mixture was stirred at room temp for 1 h after which TLC analysis indicated no starting

material. The reaction mixture was then treated with 5-amino tert-butyl-1-methylpyrazole (0.165 g, 1.08 mmol) and stirred at 40-45 °C overnight. The

reaction

mixture was cooled to room temp and purified by column chromatography (gradient

from 20% acetone/80% CH₂O₂ to 60% acetone/40% CH₂O₂) and the resulting solids were crystallized (Et₂O) to afford the desired urea (0.227 g, 58%): TLC (4% MeOH/96% CH₂O₂) R_f 0-15; ¹H-NMR (DMSO-d₆) δ 1.19 (s, 9H), 3.57 (s, 3H), 3.89 (s, 2H), 6.02 (s, 1H), 7.14 (d, J=8.4 Hz, 2H), 7.21 (d, J=6 Hz, 2H), 7.37 (d, J=8.4 Hz, 2H), 8.42 (m, 3H), 8.81 (s, 1H); FAB-MS m/z 364 (M+H)⁺.

N

N%

N N O

H H H

N-(3-tert-Butyl pyrazolyl)-N]-(3-(2-benzothiazolyloxy)phenyl)urea: A solution of 3-(2-benzothiazolyloxy)aniline (0.24 g, 1.0 mmol, 1.0 equiv) and N,N'-carbonyldiimidazole (0.162 g, 1.0 mmol, 1.0 equiv) in toluene (10 mL) was stirred at

room temp for 1 h. 5-Amino tert-butylpyrazole (0.139 g, 1.0 mmol) was added and

the resulting mixture was heated at the reflux temp. overnight. The resulting mixture

was poured into water and extracted with CH₂O₂ (3 x 50 mL). The combined organic

layers were concentrated under reduced pressure and dissolved in a minimal amount

of CH₂O₂- Petroleum ether was added and resulting white precipitate was resubmitted to the crystallization protocol to afford the desired product (0.015 g, 4%).

mp 110-111 °C; TLC (5% acetone/95% CH₂O₂) R_f 0.05; ¹H-NMR (DMSO-d₆) δ 1.24 (s, 9H), 5.97 (s, 1H), 7.704 (m, 1H), 7.744 (m, 4H), 7.68 (d, J=5.5 Hz, 1H),

7.92 (d, J=7.7 Hz, 1H), 7.70 (s, 1H), 8.95 (s, 1H), 9.34 (br s, 1H), 11.98 (br s, 1H);

EI-MS m/z 408 (M).

C4c. Reaction of a Heterocyclic Amine with Phosgene to Form an Isocyanate Followed by Reaction with Substituted Aniline

O O

N

N)] N<)]

H H

N-(5-tert-Butyl thienyl)-N]-(4-(4-pyridinyloxy)phenyl)urea: To an ice cold solution phosgene (1.93M in toluene; 0.92 mL, 1.77 mmol) in CH₂O₂ (5 mL) was added a solution of 4-(4-pyridinyloxy)aniline (0.30 g, 1.61 mmol) and pyridine (0.255

g, 3.22 mmol) in CH₂O₂ (5 mL). The resulting mixture was allowed to warm to room

temp. and was stirred for 1 h, then was concentrated under reduced pressure. The

residue was dissolved in CH₂O₂ (5 mL), then treated with 5-tert-C₅, General Method for the Reaction of a Substituted Aniline with Triphosgene Followed by Reaction with a Second Substituted Amine

O

N)]N

H H

N-(3-tert-Butyl 4-methyl isoxazolyl)-N]-(2-fluorenyl)urea: To a solution of triphosgene (55 mg, 0.185 mmol, 0.37eq) in 1,2-dichloroethane (1.0 mL) was added a

solution of 5-amino methyl tert-butylisoxazole (77.1 mg, 0.50 mmol, 1.0 eq) and diisopropylethylamine (0.104 mL, 0.60 mmol, 1.2 eq) in 1,2-dichloroethane (1.0 mL).

The reaction mixture was stirred at 70 °C for 2 h, cooled to room temp., and treated with a solution of 2-aminofluorene (30.6 mg, 0.50 mmol, 1.0 eq) and diisopropylethylamine (0.087 mL, 1.0 eq) in 1,2-dichloroethane (1.0 mL). The reaction mixture was stirred at 40 °C for 3 h and then at RT for 17 h to produce a precipitate. The solids were washed with Et₂O and hexanes to give the desired urea as a beige solid (25 mg, 14%): mp 179-181 °C; ¹H-NMR (DMSO-d₆) δ 1.28 (s, 9H), 2.47 (s, 3H), 3.86 (s, 2H), 7.22 (t, J=7.3 Hz, 1H), 7.34 (m, 2H), 7.51 (d, J=7.3 Hz, 1H), 7.76 (m, 3H), 8.89 (s, 1H), 9.03 (s, 1H); HPLC ES-MS m/z 362 ((M+H)⁺).

S

N 3/

Step 1. 5-Methyl (azidocarbonyl)thiophene: To a solution of 5-Methyl thiophenecarboxylic acid (1.06 g, 7.5 mmol) and Et₃N (1.25 mL, 9.0 mmol) in acetone (50 mL) at -10 °C was slowly added ethyl chloroformate (1.07 mL, 11.2 mmol) to keep the internal temperature below 5 °C. A solution of sodium azide (0.83 g, 12.7 mmol) in water (6 mL) was added and the reaction mixture was stirred for 2 h at 0 °C. The resulting mixture was diluted with CH₂Cl₂ (10 mL) and washed with a saturated NaCl solution (10 mL). The aqueous layer was back-extracted with CH₂Cl₂ (10 mL), and the combined organic layers were dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography (10% EtOAc/ 90% hexanes) to give the azidoester (0.94 g, 75%). Azidoester (100 mg, 0.6 mmol) in anhydrous toluene (10 mL) was heated to reflux for 1 h then cooled to rt. This solution was used as a stock solution for subsequent reactions.

OCN S

_1 :]/

Step 2. 5-Methyl thiophene Isocyanate: 5-Methyl (azidocarbonyl)thiophene (0.100 g, 0.598 mmol) in anhydrous toluene (10 mL) was heated at the reflux temp. for 1 h then cooled to room temp. This solution was used as a stock solution for subsequent reactions.

O

N N)] N j]J

H H

Step 3. N-(5-tert-Butyl isoxazolyl)-N'-(5-methyl thienyl)urea: To a solution of 5-methyl thiophene isocyanate (0.598 mmol) in toluene (10 mL) at room temp.

was added 3-amino tert-butylisoxazole (0.092 g, 0.658 mmol) and the resulting mixture was stirred overnight. The reaction mixture was diluted with EtOAc (50 mL)

and sequentially washed with a 1 N HO solution (2 x 25 mL) and a saturated NaCl solution (25 mL), dried (MgSO₄), and concentrated under reduced pressure. The residue was purified by WLC (20% EtOAc/80% hexane) to give the desired urea (0.156 g, 93%): mp 200-201 °C; TLC (20% EtOAc/80% hexane) R_f 0.20; EI-MS m/z 368 (M).

C7. General Methods for Urea Formation by Curtius Rearrangement and Isocyanate Trapping

C

CHO

Step 1. 3-Chloro-4,4-dimethylpent enal: POC13 (67.2 mL, 0.72 mol) was added to cooled (0 °C) DMF (60.6 mL, 0.78 mol) at rate to keep the internal temperature

below 20 °C. The viscous slurry was heated until solids melted (approximately 40

°C), then pinacolone (37.5 mL, 0.30 mol) was added in one portion. The reaction

mixture was then to 55 °C for 2h and to 75 °C for an additional 2 h. The resulting

mixture was allowed to cool to room temp., then was treated with THF (200 mL) and

water (200 mL), stirred vigorously for 3 h, and extracted with EtOAc (500 mL). The

organic layer was washed with a saturated NaCl solution (200 mL), (dried (Na₂SO₄)

and concentrated under reduced pressure. The residue was filtered through a pad of

silica (CH202) to give the desired aldehyde as an orange oil (15.5 g, 35%): TLC (5%

EtOAc/95% hexane) R_f 0.54; ¹H NMR (CDCl₃) δ 1.26 (s, 9H), 6.15 (d, J=7.0 Hz, 1H), 10.05 (d, J=6.6 Hz, 1H).

S

CO₂Me

Step 2. Methyl 5-tert-butyl thiophenecarboxylate: To a solution of 3-chloro-4,4-dimethylpent enal (1.93 g, 13.2 mmol) in anh. DUT (60 mL) was added a solution of Na₂S (1.23 g, 15.8 mmol) in water (10 mL). The resulting mixture was

stirred at room temp. for 15 min to generate a white precipitate, then the slurry was

treated with methyl bromoacetate (2.42 g, 15.8 mmol) to slowly dissolve the solids.

The reaction mixture was stirred at room temp. for 1.5 h, then treated with a 1 N HCl

solution (200 mL) and stirred for 1 h. The resulting solution was extracted with

EtOAc (300 mL). The organic phase was sequentially washed with a 1 N HCl solution (200 mL), water (2 x 200 mL) and a saturated NaCl solution (200 mL), dried

S

CO₂H

Step 3. 5-tert-Butyl thiophenecarboxylic acid: Methyl 5-tert-butyl thiophenecarboxylate (0.10 g, 0.51 mmol) was added to a KOH solution (0.33 M in

90% MeOH/10% water, 2.4 mL, 0.80 mmol) and the resulting mixture was heated at

to the reflux temperature for 3 h. EtOAc (5 mL) was added to the reaction

mixture; then the pH was adjusted to approximately 3 using a 1 N HCl solution. The resulting organic phase was washed with water (5 mL), dried (Na₂SO₄), and concentrated under reduced pressure (0.4 mmHg) to give the desired carboxylic acid as a yellow solid

(0.067 g, 73%): TLC (20% EtOAc/79.5% hexane/0.5% AcOH) R_f 0.29; ¹H NMR (CDCl₃) δ 1.41 (s, 9H), 6.89 (d, J=17 Hz, 1H), 7.73 (d, J=3.7 Hz, 1H), 12.30 (br s, 1H); ¹³C NMR (CDCl₃) δ 32.1 (3Q) 35.2] 122.9] 129.21 135.1, 167.5, 168

S 0

N)] N CI

H H CI

Step 4. N-(5-tert-Butyl thienyl)-N'-(2,3-dichlorophenyl)urea: A mixture of 5-tert-butyl thiophenecarboxylic acid (0.066 g, 0.036 mmol), DPPA (0.109 g, 0.39

mmol) and Et₃N (0.040 g, 0.39 mmol) in toluene (4 mL) was heated to 80 °C for 2 h,

2,3-dichloroaniline (0.116 g, 0.72 mmol) was added, and the reaction mixture was

heated to 80 °C for an additional 2 h. The resulting mixture was allowed to cool to

room temp. and treated with EtOAc (50 mL). The organic layer was washed with a 1

N HCl solution (3 x 50 mL), a saturated NaHCO₃ solution (50 mL), and a saturated

NaCl solution (50 mL), dried (Na₂SO₄), and concentrated under reduced pressure.

The residue was purified by column chromatography (5% EtOAc/95% hexane) to afford the desired urea as a purple solid (0.030 g, 24%): TLC (10% EtOAc/90% hexane) R_f 0.28; ¹H NMR (CDCl₃) δ 1.34 (s, 9H), 6.59 (br s, 2H), 7.73 (m, 2H),

.66 (br s, 1H), 8.13 (dd, J=2.9, 7.8 Hz, 1H); ¹³C NMR (CDCl₃) δ 32.2 (3Q) 34.6] 117.4, 119.0', 119.1'] 119.29 121.5, 124.4, 127.61 132.69 135.2, 136.6, 153.4; HPLC

ES-MS m/z (rel abundance) 343 ((M+H)⁺, 100%) 345 ((M+H+2)⁺, 67%), 347 ((M+H+4)⁺, 14%).

C8. Combinatorial Method for the Synthesis of Diphenyl Ureas Using Triphosgene

One of the anilines to be coupled was dissolved in dichloroethane (0.10 M). This

solution was added to a 8 mL vial (0.5 mL) containing dichloroethane (1 mL). To this

was added a triphosgene solution (0.12 M in dichloroethane, 0.2 mL, 0.4 equiv.),

followed by diisopropylethylamine (0.35 M in dichloroethane, 0.2 mL, 1.2 equiv.).

The vial was capped and heat at 80 °C for 5 h, then allowed to cool to room temp for

approximately 10 h. The second aniline was added (0.10 M in dichloroethane, 0.5

mL, 1.0 equiv.), followed by diisopropylethylamine (0.35 M in dichloroethane, 0.2

mL, 1.2 equiv.). The resulting mixture was heated at 80 °C for 4 h, cooled to room

temperature and treated with MeOH (0.5 mL). The resulting mixture was

concentrated under reduced pressure and the products were purified by reverse phase HPLC.

2o D, Misc. Methods of Urea Synthesis

DI. Electrophilic Halogenation

0

N N[:.

Br H H

N-(2-Bromo tert-butyl thienyl)-N]-(4-methylphenyl)urea: To a slurry of N-(5-tert-butyl thienyl)-N]-(4-methylphenyl)urea (0.50 g, 1.7 mmol) in CHCl₃ (20 mL)

at room temp was slowly added a solution of Br₂ (0.09 mL, 1.7 mmol) in CHCl₃ (10

mL) via addition funnel causing the reaction mixture to become homogeneous.

Stirring was continued 20 min after which TLC analysis indicated complete reaction.

The reaction was concentrated under reduced pressure, and the residue triturated (2 x

Et₂O/hexane) to give the brominated product as a tan powder (0.43 g, 76%): mp 161-

163 °C; TLC (20% EtOAc/ 80% hexane) R_f 0.71; ¹H NMR (DMSO-d₆) δ 1.29 (s, 9H), 2.22 (s, 3H), 7.07 (d, J=8.46 Hz, 2H), 7.31 (d, J=8.46 Hz, 2H), 7.38 (s, 1H), 8.19

(s, 1H), 9.02 (s, 1H); ¹³C NMR (DMSO-d₆) δ 20.3, 31.6 (3Q, 34.7,

89.6, 117.5, 118.1

(2Qq 129.2 (2Qq 130.89 136.09 136.9, 151.8, 155.2; FAB-MS m/z (rel abundance) 367

((M+H)+7 98%)] 369 (M+2+H)+g I 00%).

D2, Synthesis of o)-Alkoxy Ureas

0 0

N)]N H

H H

Step 1. N-(5-tert-Butyl thienyl)-N]-(4-(4-hydroxyphenyl)oxyphenyl)urea: A solution of N-(5-tert-butyl thienyl)-N-(4-(4-methoxyphenyl)oxyphenyl)urea (1.2 g,

3 mmol) in CH₂Cl₂ (50 mL) was cooled to -78 °C and treated with BBr₃ (1.0 M in CH₂Cl₂) 4.5 mL, 4.5 mmol, 1.5 equiv) dropwise via syringe. The resulting bright

yellow mixture was warmed slowly to room temp and stirred overnight. The resulting

mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (50 mL), then washed with a saturated NaHCO₃ solution (50 mL) and a saturated NaCl solution (50 mL), dried (Na₂SO₄), and concentrated under reduced

pressure. The residue was purified via flash chromatography (gradient from 10%

EtOAc/90% hexane to 25% EtOAc/75% hexane) to give the desired phenol as a tan foam (1.1 g, 92%): TLC (20% EtOAc/80% hexane) R_f 0.23; ¹H NMR (DMSO-d₆) δ 1.30 (s, 9H), 6.84 (m, 7H), 6.97 (d, J=1.47 Hz, 1H), 7.37 (dm, J=9.19 Hz, 2H),

8.49 (s, 1H), 8.69 (s, 1H), 9.25 (s, 1H); FAB-MS m/z (rel abundance) 383

((M+H)+,

2o 33%).

0 0

N)]N

H H

Step 2. N-(5-tert-Butyl thienyl)-N]-(4-(4-ethoxyphenyl)oxyphenyl)urea: To a mixture of N-(5-tert-butyl thienyl)-N]-(4-(4-hydroxyphenyl)oxyphenyl)urea (0.20

gq 0.5 mmol) and CS₂CO₃ (0.18 gq 0.55 mmol, 1.1 equiv) in reagent grade acetone (10

mL) was added ethyl iodide (0.08 mL, 1.0 mmol, 2 equiv) via syringe, and the resulting slurry was heated at the reflux temp. for 17 h. The reaction was cooled,

filtered, and the solids were washed with EtOAc. The combined organics were concentrated under reduced pressure, and the residue was purified via preparative

HPLC (60% CH₃CN/40% H₂O/0.05% TFA) to give the desired urea as a colorless powder (0.16 g, 73%): mp 155-156 °C; TLC (20% EtOAc/ 80% hexane) R_f 0.40; ¹H-

NMR (DMSO-d₆) 5 1.30 (s, 9H), 1.30 (t, J=6.99 Hz, 3H), 3.97 (q, J=6.99 Hz, 2H),

6.80 (d, J=1.47 Hz, 1H), 6.86 (dm, J=8.82 Hz, 2H), 6.90 (s, 4H), 6.98 (d, J=1.47, 1H),

7.40 (dm, J=8.83 Hz, 2H), 8.54 (s, 1H), 8.73 (s, 1H); ¹³C-NMR (DMSO-d₆) 8 14.7,

32.0 (3Q9 33.91 63.39 102.59 115.5 (2Q9 116.3] 118.4 (2Q9 119.7 (2C), 119.8 (2Q]

135.09 136.39 150.49 152.19 152.49 154.4, 154.7; FAB-MS m/z (rel abundance) 411

((M+H)+] 15%).

io D3. Synthesis of o)-Carbamoyl Ureas

N 0 0

zz]'

N K NJ:DrIaN)t]]

H H H

N-(3-tert-Butyl-1-methyl pyrazolyl)-N]-(4-(4-acetaminophenyl)methylphenyl)urea: To a solution of N-(3-tert-butyl-1-methyl pyrazolyl)-N]-(4-(4-aminophenyl)methylphenyl)urea (0.300 g, 0.795 mmol) in i5 CH₂O₂ (15 mL) at 0 °C was added acetyl chloride (0.057 mL, 0.795 mmol), followed

by anhydrous Et₃N (0.111 mL, 0.795 mmol). The solution was allowed to warm to

room temp over 4 h, then was diluted with EtOAc (200 mL). The organic layer was

sequentially washed with a 1M H₂O solution (125 mL) then water (100 mL), dried (MgSO₄), and concentrated under reduced pressure. The resulting residue was purified by filtration through a pad of silica (EtOAc) to give the desired product as a

white solid (0.160 g, 48%): TLC (EtOAc) R_f 0.33; ¹H-NMR (DMSO-d₆) 8 1.17 (s, 9H)q 1.98 (s, 3H), 3.55 (s, 3H), 3.78 (s, 2H), 6.00 (s, 1H), 7.07 (d, J=8.5 Hz, 2H), 7.09

(d, J=8.5 Hz, 2H), 7.32 (d, J=8.5 Hz, 2H), 7.44 (d, J=8.5 Hz, 2H), 8.38 (s, 1H), 8.75

(s, 1H), 9.82 (s, 1H); FAB-MS m/z 420 ((M+H)+).

D4. General Method for the Conversion of Ester-Containing Ureas into Alcohol-Containing Ureas

0

N)]N CI

H H CI

N-(]V-(2-Hydroxyethyl) tert-butyl pyrazolyl)-N]-(2,3-dichlorophenyl)urea.

A solution of N-(IV'-(2-(2,3-dichlorophenylamino)carbonyloxyethyl) tert-butyl pyrazolyl)-N'-(2,3-dichlorophenyl)urea (prepared as described in Method A.3; 0.4 g, 0.72 mmols) and NaOH (0.8 mL, 5N in water, 4.0 minoles) in EtOH (7 mL) was heated at -65 °C for 3 h at which time TLC indicated complete reaction. The reaction mixture was diluted with EtOAc (25 mL) and acidified with a 2N HO solution (3 mL). The resulting organic phase was washed with a saturated NaCl solution (25 mL), dried (MgSO₄) and concentrated under reduced pressure. The residue was crystallized (Et₂O) to afford the desired product as a white solid (0.17 g, 64 %): TLC (60% EtOAc/40% hexane) R_f 0.16; ¹H-NMR (DMSO-d₆) δ 1.23 (s, 9H), 3.70 (t, J=5.7 Hz, 2H), 4.10 (t, J=5.7 Hz, 2H), 6.23 (s, 1H), 7.32 (in, 2H), 8.09 (in, 1H), 9.00 (br s, 1H), 9.70 (br s, 1H); FAB-MS m/z (rel abundance) 371 ((M+H)⁺, 100%).

D5a. General Method for the Conversion of Ester-Containing Ureas into 2o Amide-Containing Ureas

0
N%
N N CI
HOSrj H H CI
0

Step 1. N-(N'-(Carboxymethyl) tert-butyl pyrazolyl)-N]-(2,3-dichlorophenyl)urea: A solution of N-(IV'-(ethoxycarbonylinethyl) tert-butyl pyrazolyl)-N'-(2,3-dichlorophenyl)urea (prepared as described in Method A3, 0.46 g, 1.11 mmols) and NaOH (1.2 mL, 5N in water, 6.0 mmols) in EtOH (7 mL) was stirred at room temp. for 2 h at which time TLC indicated complete reaction. The reaction mixture was diluted with EtOAc (25 mL) and acidified with a 2N HO solution (4 mL). The resulting organic phase was washed with a saturated NaCl solution (25 mL), dried (MgSO₄) and concentrated under reduced pressure. The residue was crystallized (Et₂O/hexane) to afford the desired product as a white solid (0.38 g, 89%): TLC (10% MeOH/90% CH₂Cl₂) R_f 0.04; ¹H-NMR (DMSO-d₆) δ 1.21 (s, 9H), 4.81 (s, 2H), 6.19 (s, 1H), 7.35 (m, 2H), 8.12 (m, 1H), 8.76 (br s, 1H), 9.52 (br s, 1H); FAB-MS m/z (rel abundance) 385 ((M+H)⁺, 100%).

0
N%
N N CI
MeHN H H CI
0

Step 2. N-(V-((Methylcarbamoyl)methyl) tert-butyl pyrazolyl)-N]-(2,3-dichlorophenyl)urea: A solution of N-(N'-(carboxymethyl) tert-butyl pyrazolyl)-N'-(2,3-dichlorophenyl)urea (100 mg, 0.26 mmole) and NN]-carbonyldiimidazole (45 mg, 0.28 mmole) in CH₂Cl₂ (10 mL) was stirred at room temp. 4 h at which time TLC indicated formation of the corresponding anhydride (TLC (50% acetone/50% CH₂Cl₂) R_f 0.81). Dry methylamine hydrochloride (28 mg, 0.41 mmole) was then added followed by diisopropylethylamine (0.07 mL, 0.40 mmole). The reaction mixture was stirred at room temp. overnight, then diluted with

CH202, washed with water (30 mL), a saturated NaCl solution (30 mL), dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (gradient from 10% acetone/90% CH₂O₂ to 40% acetone/60% CH₂O₂) and the residue was crystallized (Et₂O/hexane) to afford the desired product (47 mg, 46%): TLC (60% acetone/40% CH₂O₂) R_f 0.59; ¹H-NMR (DMSO-d₆) δ 1.20 (s, 9H), 2.63 (d, J=4.5 Hz, 3H), 4.59 (s, 2H), 6.15 (s, 1H), 7.34 (m, 2H), 8.12 (m, 2H), 8.79 (br s, 1H), 9.20 (br s, 1H); FAB-MS m/z (rel abundance) 398 ((M+H)⁺, 30%).

D5b. General Method for the Conversion of Ester-Containing Ureas into Amide-Containing Ureas

O O

N N)]N CO₂H

H H

Step 1. N-(5-tert-Butyl isoxazolyl)-N]-(4-(4-carboxyphenyl)oxyphenyl)urea.

To a solution of N-(5-tert-butyl isoxazolyl)-N]-(4-(4-ethoxyoxycarbonylphenyl)-oxyphenyl)urea (0.524 g, 1.24 mmol) in a mixture of EtOH (4 mL) and THF (4 mL) was added a 1M NaOH solution (2 mL) and the resulting solution was allowed to stir overnight at room temp. The resulting mixture was diluted with water (20 mL) and treated with a 3M HCl solution (20 mL) to form a white precipitate. The solids were washed with water (50 mL) and hexane (50 mL), and then dried (approximately 0.4 mmHg) to afford the desired product (0.368 g, 75 %). This material was carried to the next step without further purification.

O O

Zl]' I NHMe

N H H

N N

O

Step 2. N-(5-tert-Butyl isoxazolyl)-N]-(4-(4-(N-methylcarbamoyl)-phenyl)oxyphenyl)urea: A solution of N-(5-tert-butyl isoxazolyl)-N-(4-(4-carboxyphenyl)oxyphenyl)urea (0.100 g, 0.25 mmol), methylamine (2.0 M in TBF; 0.140 mL, 0.278 mmol), 1-ethyl (3-dimethylaminopropyl)carbodiimide hydrochloride (76 mg, 0.39 mmol), and N-methylnorpholine (0.030 mL, 0.27 mmol) in a mixture of TBF (3 mL) and DW (3mL) was allowed to stir overnight at room temp. then was poured into a 1M citric acid solution (20 mL) and extracted with EtOAc (3 x 15 mL). The combined extracts were sequentially washed with water (3 x 10 mL) and a saturated NaCl solution (2 x 10 mL), dried (Na₂SO₄ filtered, and concentrated in vacuo. The resulting crude oil was purified by flash chromatography (60 % EtOAc/40% hexane) to afford the desired product as a white solid (42 mg, 40%): EI-MS m/z 409 ((M+H)⁺).

D6. General Method for the Conversion of co-Amine-Containing Ureas into

Amide-Containing Ureas

O O

N N] N NH₂

H H

N-(5-tert-Butyl isoxazolyl)-N]-(4-(4-aminophenyl)oxyphenyl)urea: To a solution of N-(5-tert-butyl isoxazolyl)-N]-(4-(4-tert-butoxycarbonylaminophenyl)oxyphenyl)-urea (prepared in a manner analogous to Methods B6 then C2b; 0.050 g, 0.11 mmol) in anhydrous 1,4-dioxane (3 mL) was added a concentrated HCl solution (1 mL) in one portion and the mixture was allowed to stir overnight at room temperature. The mixture was then poured into water (10 mL) and EtOAc (10 mL) and made basic using a 1M NaOH solution (5 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL).

The combined organic layers were sequentially washed with water (3 x 100 mL) and a saturated NaCl solution (2 x 100 mL), dried (Na₂SO₄), and concentrated in vacuo to afford the desired product as a white solid (26 mg, 66%). EI-MS m/z 367 ((M+H)⁺).

D7, General Method for the Oxidation of Pyridine-Containing Ureas

O

N]

O

N N N'I:::D

H H

N-(5-tert-Butyl isoxazolyl)-N]-(4-(N-oxo4-pyridinyl)methylphenyl)urea: To a solution of N-(5-tert-butyl isoxazolyl)-N]-(4-(4-pyridinyl)methylphenyl)urea (0.100 g, 0.29 mmol) in CHCl₃ (10 mL) was added m-CPBA (70% pure, 0.155 g, 0.63 mmol) and the resulting solution was stirred at room temperature for 16 h. The reaction mixture was then treated with a saturated K₂CO₃ solution (10 mL). After 5 min, the solution was diluted with CHCl₃ (50 mL). The organic layer was washed successively with a saturated aqueous NaHSO₃ solution (25 mL), a saturated NaHCO₃ solution (25 mL) and a saturated NaCl solution (25 mL), dried (MgSO₄), and concentrated in vacuo. The residual solid was purified by MPLC (15% MeOH/85% EtOAc) to give the N-oxide (0.082 g, 79%).

D8. General Method for the Acylation of a Hydroxy-Containing Urea

O O O

N

N N

H H

N-(5-tert-Butyl isoxazolyl)-N]-(4-(4-acetoxyphenyloxy)phenyl)urea: To a solution of N-(5-tert-butyl isoxazolyl)-N]-(4-(4-hydroxyphenyloxy)phenyl)urea (0.100 g, 0.272 mmol), NN-dimethylaminopyridine (0.003 g, 0.027 mmol) and Et₃N (0.075 mL, 0.544 mmol) in anhydrous TBF (5 mL) was added acetic anhydride (0.028 mL, 0.299 mmol), and the resulting mixture was stirred at room temperature for 5 h. The resulting mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (10 mL). The resulting solution was sequentially washed with a 5% citric acid solution (10 mL), a saturated NaHCO₃ solution (10 mL) and a

saturated
NaCl solution (10 mL), dried (Na₂SO₄), and concentrated under reduced
pressure to
give an oil which slowly solidified to a glass (0.104 g, 93%) on standing
under
reduced pressure (approximately 0.4 mmHg): TLC (40% EtOAc/60% hexane) R_f
0.55; FAB-MS m/z 410 ((M+H)⁺).

D9. Synthesis of (o-Alkoxy)pyridines

O O

oo]

N N N N O

H H H

Step 1. N-(5-tert-Butyl isoxazolyl)-N]-(4-(2(1H)-pyridinon yl)oxyphenyl)-
urea: A solution of N-(5-tert-butyl isoxazolyl)-N-(4-(5-(2-methoxy)pyridyl)-
oxyaniline (prepared in a manner analogous to that described in Methods B3k
and
C3b; 1.2 g, 3.14 mmol) and trimethylsilyl. iodide (0.89 mL, 6.28 mmol) in
CH₂O₂
(30 mL) was allowed to stir overnight at room temp., then was to 40 °C for 2
h. The
resulting mixture was concentrated under reduced pressure and the residue was
purified by column chromatography (gradient from 80% EtOAc/20% hexane to 15%
MeOH/85% EtOAc) to give the desired product (0.87 g, 75%): mp 175-180 °C; TLC
(80% EtOAc/20% hexane) R_f 0.05; FAB-MS m/z 369 ((M+H)⁺+5 100%).

N N Nj::r OEt

H H

Step 2. N-(5-tert-Butyl isoxazolyl)-N]-(4-(5-(2-Ethoxy)pyridyl)oxyphenyl)urea

A slurry of N-(5-tert-butyl isoxazolyl)-N-(4-(2(1H)-pyridinon
yl)oxyphenyl)urea

(0.1 g, 0.27 mmol) and Ag₂CO₃ (0.05 g, 0.18 mmol) in benzene (3 mL) was
stirred at

room temp. for 10 min. Iodoethane (0.023 mL, 0.285 mmol) was added and the
resulting mixture was heated at the reflux temp. in dark overnight. The
reaction

mixture was allowed to cool to room temp., and was filtered through a plug of
Celite OD

then concentrated under reduced pressure. The residue was purified by column
chromatography (gradient from 25% EtOAc/75% hexane to 40% EtOAc/60% hexane)
to afford the desired product (0.041 g, 38%): mp 146 °C; TLC (40%
EtOAc/60%

hexane) R_f 0.49; FAB-MS m/z 397 ((M+H)⁺) 100%).

D10, Reduction of an Aldehyde- or Ketone-Containing Urea to a Hydroxide- Containing Urea

O O

N N)] NZr IDY

1 5 H H OH

N-(5-tert-Butyl isoxazolyl)-N]-(4-(4-(1-hydroxyethyl)phenyl)oxyphenyl)urea.

To a solution of N-(5-tert-butyl isoxazolyl)-N]-(4-(4-(1-
acetylphenyl)oxyphenyl)urea (prepared in a manner analogous to that described
in

Methods B1 and C2b; 0.060 g, 0.15 mmol) in MeOH (10 mL) was added NaBH₄
(0.008 g, 0.21 mmol) in one portion. The mixture was allowed to stir for 2 h
at room

temp., then was concentrated in vacuo. Water (20 mL) and a 3M HCl solution (2

m.L)

were added and the resulting mixture was extracted with EtOAc (3 x 20 mL).

The

combined organic layers were washed with water (3 x 10 mL) and a saturated NaCl

solution (2 x 10 mL), dried (MgSO₄), and concentrated in vacuo. The

resulting white

solid was purified by trituration (Et₂O/hexane) to afford the desired product

(0.021 g, .

32 %): mp 80-85 °C; ¹H NMR (DMSO-d₆) δ 1.26 (s, 9H), 2.50 (s, 3H), 4.67 (m, 1H),

5.10 (br s, 1H), 6.45 (s, 1H), 6.90 (m, 4H), 7.29 (d, J = 0 Hz, 2H), 7.42 (d, J = 9.0 Hz,

2H) q 8.76 (s, 1H), 9.44 (s, 1H); HPLC ES-MS m/z 396 ((M+H)⁺).

D11: Synthesis of Nitrogen-Substituted Ureas by Curtius Rearrangement of Carboxy-Substituted Ureas

H

0 N 0 N]] Ph

0 Y

oe;:] 0

N N Nicr 101o]

H H

N-(5-tert-Butyl isoxazolyl)-N]-(4-(3-(benzyloxycarbonylamino)phenyl)-oxyphenyl)urea: To a solution of the N-(5-tert-butyl isoxazolyl)-N-(4-(3-carboxyphenyl)oxyphenyl)urea (prepared in a manner analogous to that described in

Methods B3a, Step 2 and C2b; 1.0 g, 2.5 mmol) in anhydrous toluene (20 mL) was added

Et₃N (0.395 mL, 2.8 mmol) and DPPA (0.610 mL, 2.8 mmol). The mixture was heated at 80 °C with stirring for 1.5 h then allowed to cool to room temp.

Benzyl

alcohol (0.370 mL, 3.5 mmol) was added and the mixture was heated at 80 °C with

stirring for 3 h then allowed to cool to room temp. The resulting mixture was poured

into a 10% HOAc solution (50 mL) and the resulting solution extracted with EtOAc (3 x

50 mL). The combined organic layers were washed with water (3 x 50 mL) and a saturated NaCl (2 x 50 mL), dried (Na₂SO₄), and concentrated in vacuo. The crude

oil was purified by column chromatography (30% EtOAc/70% hexane) to afford the

desired product as a white solid (0.7 g, 60 %): mp 73-75 °C; ¹H NMR (DMSO-d₆) δ

1.26 (s, 9H), 5.10 (s, 2H), 6.46 (s, 1H), 6.55 (d, J = 7.0 Hz, 1H), 6.94 (d, J = 7.0 Hz,

2H), 7.70 (m, 7H), 8.78 (s, 1H), 9.46 (s, 1H), 9.81 (s, 1H); HPLC ES-MS m/z

501

((M+H)⁺).

The following compounds have been synthesized according to the General Methods

listed above.

Table 1. 5-Substituted isoxazolyl Ureas

R₁

0

0 2

)] R

N N

H H

EX. R1 R' mp TLC Solvent Mass Synth.

(C) Rf System Spec. Source Method

I t-Bu F 169- 0.45 25% 357 FAB Clb

172 EtOAc / (M+H)+

75%

hexane

2 t-Bu Me Me 0.63 5% 288 FAB C2a

MeOH / (M+H)+

95%

CH₂Cl₂

3 t-Bu 169- 424 FAB Qb] D2

Jr 0 OBU-n

f \.-/- _& 171 (M+H)+

4 t-Bu 0.19 50% 423 FAB C2bq D3

NH

]=O EtOAc (M+H)+

Et 50%

hexane

5 t-Bu 202- 0.15 60% 409 FAB C2b] D3

NH

/]=O 206 EtOAc (M+H)+

Me 40%

1 hexane

6 t-Bu 214- 0.75 60% 463 FAB Ub] D3

NH

]=O 217 EtOAc / (M+H)+

F3C 40%

hexane

7 t-Bu 0-&OBn 157 0.42 40% 458 FAB B3a,

EtOAc / (M+H)+ C2b

60%

hexane

8 t-Bu 148- 352 FAB CIC

149 (M+H)+

9 t-Bu Cl Cl 0.12 20% 329 BPLC/ CIC

EtOAc (M+H)+ ES-MS

80%

hexane

10 t-Bu Cl 176- 0.50 30% 400 (M+) BpLC/ C2b

177 EtOAc ES-MS

70%

hexane

I I t-Bu 156- 0.50 30% 366 BPLC/ C2b

157 EtOAc (M+H)+ ES-MS

70%

hexane

12 t-Bu 190- 0.15 30% 350 (M+) EI C2b

C! C\N 191 EtOAc

70%

hexane

t-Bu 175- 0.25 30% 409 HPLC/ DU

N 177 EtOAc (M+H)+ ES-MS Step I

O___], 1 70% B3b

S:0] hexane Step 2,

C2b

14 t-Bu 0 0.35 30% 402 HPLC/ B3bj

EtOAc (M+H)+ ES-MS C2b

70%
 hexane
 15 t-Bu 0.1 10% 350 HPLC/ C2b
 MeOH (M+H)+ ES-MS
 0 90%
 CH202
 16 t-Bu ____ao_C 15% 352 (M+) EI C2b
 N 240- 0.2
 243 MeOH /
 85%
 I EtOAc
 17 t-Bu --&O-&OH 0.15 30% 367 (M+) EI B3a,
 EtOAc / C2b, D2
 70% Step 1
 hexane
 18 t-Bu S- C\N 178- 368 (M+) EI B4a,
 I 179 1 1 C2b
 19 t-Bu H2 N .25 30% 351 FAB B1] C2b
 CLoN 164- 0
 165 EtOAc / (M+H)+
 70%
 hexane
 20 t-Bu --- aH N 170- 0.15 30% 351 FAB B71 B12
 c 172 EtOAc / (M+H)+ C2b
 70%
 hexane
 21 t-Bu HO 0.3 25% 368 FAB C2b
 0 EtOAc / (M+H)+
 75%
 hexane
 22 t-Bu H2 188- 367 FAB D7
 ____&CLC\N-a, -o 191 (M+H)+
 23 t-Bu Me 0.8 25% 366 FAB B3a,
 EtOAc / (M+H)+ C2b
 75%
 hexane
 24 t-Bu _JF] \O-&OMe 155- 0.55 30% 382 FAB B3a,
 156 EtOAc / (M+H)+ C2b
 70%
 hexane
 25 t-Bu 145- 0.6 25% 438 FAB B3a,
 0
 -&OArn-n 148 EtOAc / (M+H)+ C2b, D2
 75%
 hexane
 26 t-Bu -1/-\\-o OPr-n 137- 0.62 25% 410 FAB B3a,
 141 EtOAc / (M+H)+ C2bq D2
 75%
 hexane
 t-Bu --//] \]O_&opr_j 164- 0.6 25% 410 FAB B3a,
 166 EtOAc / (M+H)+ Ub] D2
 75%
 hexane
 28 t-Bu --//---% &OBu-i 69- 0.6 25% 424 FAB B3a,
 7 1 EtOAc / (M+H)+ MI D2
 75%
 hexane
 29 t-Bu OH 78- 0.15 25% 368 FAB C2b
 0 80 EtOAc (M+H)+
 75%

hexane
 30 t-Bu 0 235 0.35 25% 402 FAB Wb]
 EtOAc (M+H)+ C2b
 75%
 hexane
 3 1 t-Bu s 201- 0.35 25% 418 FAB B3bq
 202 EtOAc (M+H)+ C2b
 75%
 hexane
 32 t-Bu 158- 0.25 30% 369 FAB B4a,
 159 EtOAc (M+H)+ C2b
 S- C\N 70%
 hexane
 33 t-Bu CF3 180- 0.15 30% 437 FAB Wb]
 ._]S_C 181 EtOAc / (M+H)+ C2b
 N 70%
 1 hexane
 34 t-Bu N 68- 0.3 50% 370 FAB B4a,
 s 71 EtOAc / (M+H)+ C2b
 -a --O\T
 N 50%
 hexane
 35 t-Bu N 159- 0.2 50% 370 FAB B4a,
 S.- C\ - /) 161 EtOAc / (M+H)+ C2b
 N 50%
 1hexane
 36 t-Bu S_.&C, 183. 0.3 30% 403 FAB C2b
 186 EtOAc / (M+H)+
 N 70%
 hexane
 37 t-Bu F3C 98- 0.25 10% 454 FAB C2b
 cl 101 EtOAc / (M+H)+
 90%
 hexane
 38 t-Bu 163- 0.25 20% 394 FAB B12 C2b
 -ao 166 EtOAc / (M+H)+
 80%
 hexane
 39 t-Bu O-&SMe 144- 0.3 30% 403 FAB C2b
 147 EtOAc / (M+H)+
 N
 70%
 hexane
 40 t-Bu O-&OMe 155- 0.25 10% 454 FAB C2b
 157 EtOAc (M+H)+
 N
 90%
 hexane
 t-Bu 162- 0.25 20% 394 FAB B19 C2b
 --&S-&F 164 EtOAc (M+H)+
 80%
 hexane
 42 t-Bu S--&Me 149- 0.15 15% 3 FAB C2b
 150 EtOAc (M+H)+
 85%
 hexane
 43 t-Bu N 200- 0.35 50% 354 FAB Wj]
 0 D/T
 N 201 EtOAc / (M+H)+ C2b
 50%

hexane
 44 t-Bu 77- 0.3 30% 408 (M+) El B3e,
 80 EtOAc / C2b
 N
 s 70%
 hexane
 45 t-Bu N 162- 0.17 40% 354 FAB B3jj
 o - C /)
 N 164 EtOAc (M+H)+ C2b
 60%
 hexane
 46 t-Bu N 30% 368 (M+) El B29 C2b
 73- 0.2
 76 EtOAc
 70%
 hexane
 47 t-Bu 185- 0.30 30% 413 FAB C2b
 \---/--S-&NO2 188 EtOAc (M+H)+
 70%
 hexane
 48 t-Bu S-&Pr-i 159- 410 FAB B29 C2b
 160 (M+H)+ 1
 49 t-Bu MeO 73- 0.15 25% 428 FAB B25C2b
 s 75 EtOAc (M+H)+
 --t] 75%
)Me hexane
 50 t-Bu Me 188- 0.25 5% 422 FAB B1, C2b
 0 - M e
 190 EtOAc (M+H)+
 Et 95%
 hexane
 5 1 t-Bu]\S--&OMe 143- 0.25 30% 398 FAB B3e,
 145 EtOAc (M+H)+ C2b
 70%
 hexane
 52 t-Bu s OMe 148- 0.25 30% 428 FAB B3e,
 151 EtOAc (M+H)+ C2b
 OMe 70%
 hexane
 53 t-Bu 0 - C\N 0.30 100% 353 FAB BO
 I EtOAc (M+H)+ Ob
 54 t-Bu 172- 0.25 10% 420 FAB C2b
 -F\]-O-&CF3
 174 EtOAc (M+H)+
 90%
 hexane
 55 t-Bu o OMe 126- 0.25 30% 412 FAB B3e,
 129 EtOAc (M+H)+ C2b
 OMe 70%
 hexane
 t-Bu 0 201- 0.25 10% 396 FAB B3e,
 -Q 204 EtOAc (M+H)+ C2bq D2
 oEt 90%
 hexane
 57 t-Bu N 163- 0.30 40% 369 FAB B4a,
 164 EtOAc (M+H)+ C2b
 60%
 hexane
 58 t-Bu 162- 0.20 25% 363 (M+) El C2b
 163 EtOAc

75%
 hexane
 59 t-Bu 0 N 127- 0.22 40% 353 FAB 133e
 129 EtOAc (M+H)+ Step 1,
 60% B29 C2b
 hexane 1
 60 t-Bu 85- 0.20 50% 402 (M+) El We
 0 -
 N 87 EtOAc / Step I 9
 50% B21 C2b
 hexane
 61 t-Bu Meo 108- 0.25 10% 381 El 133e,
 110 EtOAc / (M+H)+ C2b
 90%
 1hexane
 62 t-Bu CO2Et 153- 0.25 30% 424 FAB B3e,
 - - 0 155 EtOAc / (M+H)+ C2b
 70%
 hexane
 63 t-Bu]\o NH 117- 0.25 10% 467 FAB B69 C2b
]=o 120 EtOAc / (M+H)+
 t-BuO 90%
 1 hexane
 64 t-Bu 0 186- 0.25 30% 367 FAB 136]
 NH2 189 EtOAc / (M+H)+ MI D6
 70%
 hexane
 65 t-Bu 0 209- 0.25 60% 423 FAB B3e,
 --/F
 --\]/NW2 212 EtOAc (M+H)+ Qb]
 40% D5b
 hexane
 66 t-Bu 0
 221- 0.25 60% 409 FAB B3e,
 k-]/NHme 224 EtOAc (M+H)+ C2bq
 40% D5b
 hexane
 67 t-Bu 0 Me 114- 0.25 60% 409 FAB B3e,
 jr 0 117 EtOAc (M+H)+ Ub]
 j 40% D5b
 -A.-j d/-NH
 1hexane
 68 t-Bu 0 201- 0.25 60% 423 FAB B3e,
]-NW2 203 EtOAc (M+H)+ C2b
 40% D5b
 hexane
 69 t-Bu 145- 0.25 30% 423 (M+) El B3e,
 &Co2Et
 147 EtOAc C2b
 70%
 hexane
 t-Bu --aO-&F 148- 0.25 20% 370 FAB B3e,
 151 EtOAc / (M+H)+ C2b
 80%
 hexane
 71 t-Bu 0 188- 0.25 20% 382 FAB B3e,
 -Q 201 EtOAc / (M+H)+ C2b
 OMe 80%
 I hexane
 72 t-Bu N 134- 0.25 20% 367 FAB B3e,

0- a\ / Me 136 EtOAc / (M+H)+ C2b
 80%
 hexane
 73 t-Bu 152- 0.25 20% 396 FAB B3e,
 0
 --\OMe 155 EtOAc (M+H)+ C2b
 80%
 hexane
 74 t-Bu 0-< 176- 0.25 50% 403 FAB B3e,
 178 EtOAc (M+H)+ C2b
 N
 ,T-]]
 N- 50%
 hexane
 75 t-Bu 200 0.30 5% 396 FAB B3a
]0--&CO,H
 dec MeOH (M+H)+ Step 2,
 0.5% C2b
 AcOH
 94.5%
 CH202
 76 t-Bu 0 177- 419 FAB B89
 2 180 (M+H)+ Wb]
 C N] 10
 C2b
 0
 77 t-Bu - 0.60 60% 485 FAB C2b, D3
 NH
 >=O EtOAc (M+H)+
 CH2 40%
 0 hexane
 78 t-Bu Et 194- 0.24 5% 377 FAB Oa
 N 195 MeOH (M+H)+
 95%
 CH2C12
 79 t-Bu H 160- 0.79 75% 381 FAB C3a
 -C\ \]41-&OMe
 162 EtOAc (M+H)+
 25%
 hexane
 80 t-Bu
 140- 0.25 50% 352 (M+) E1 B4b]
 143 EtOAc Ob
 0-% N 50%
 I CH2C12
 81 t-Bu 147- 0.25 50% 352 (M+) E1 Wf]
 -Q 150 EtOAc Ob
 0- 50%
 N C11202
 82 t-Bu 166- 0.44 50% 396 FAB Ob
 o 0 170 EtOAc (M+H)+
 0 50%
 hexane
 t-Bu 175- 0.05 80% 369 FAB B3
 _Q 180 EtOAc / (M+H)+ C3bq D9
 0 : \'-o 20%
 - C\NH hexane
 84 t-Bu 190- 0.25 50% 367 FAB B3g,
 _Q N 193 EtOAc / (M+H)+ C3b
 0 - &\'/' Me 50%

I CH2C12
 85 t-Bu Me 136- 0.25 50% 367 FAB 134b,
 140 EtOAc (M+H)+ C3b
 0 - (\)N 50%
 CH202
 8 6 t-Bu Me 65- 0.25 50% 367 FAB B4b2
 67 EtOAc (M+H)+ C3b
 50%
 1 CH202
 87 t-Bu Me 68- 0.25 50% 383 FAB 134a,
 --&S-- C\N 72 EtOAc (M+H)+ C3b
 50%
 CH2C12
 88 t-Bu N 146 0.49 40% 397 FAB 133k]
 0 - a\ / OEt EtOAc (M+H)+ C3bj D9
 60%
 hexane
 89 t-Bu N 100 0.54 40% 411 FAB BR,
 0 - C\ :I
] -OPrn EtOAc (M+H)+ C3bq D9
 60%
 hexane
 90 f-Bu 0 N 100 0.62 40% 411 FAB BR7
 , _ -- -&' -i
 Opr EtOAc / (M+H)+ 0b] D9
 60%
 hexane
 9 1 t-Bu Me 164- 0.25 50% 382 (M+) E1 134a,
 165 EtOAc / C3b
 S-] \)N 50%
 CH2C12
 92 t-Bu - H2 175- 0.25 20% 485 FAB B3e,
 \ , *-C-NH 177 EtOAc (M+H)+ C3bq
 0 80% D5b
 hexane
 93 t-Bu 0 94- 0.25 20% 390 FAB B59 C3b
 97 EtOAc (M+H)+
 80%
 OEt hexane
 94 t-Bu H I T 0.30 50% (M+) E1 C3a, D2
 \ \)NI _aOH
 141 EtOAc step 1
 50%
 hexane
 95 t-Bu OH 0.15 100% 367 FAB B9, Ch
] \N EtOAc (M+H)+
 96 t-Bu NH 120- 0.25 20% 471 HPLC 133e,
 122 EtOA
 0 c/ (M+H)+ ES-MS C3bj
 80% D5b
 hexane
 t-Bu Et-NH 168- 0.25 50% 423 HPLC B3e,
 0 170 EtOAc (M+H)+ ES-MS C3bj
 50% D5b
 hexane
 98 t-Bu OH 80- 0.25 50% 396 HPLC BI,
 85 EtOAc (M+H)+ ES-MS Qb]
 50% DIO
 hexane
 99 t-Bu 0 73- 0.25 30% 501 HPLC B3a

04 75 EtOAc (M+H)+ ES-MS step 2,
 NH 70% Ub]
 hexane DI1
 100 t-Bu Br 240] 414. 414 HPLC
 DEC 95 (M+H)+ ES-MS
 3r
 101 t-Bu O OH 132- 0.52 40% 383 FAB B3a,
 134 EtOAc (M+H)+ BIq C3b
 60%
 hexane
 103 t-Bu O 0.52 100% 396 HPLC B109
]-NH2 EtOAc (M+H)+ / ES- B4bj
 __/T]\O-]\N MS C2b
 104 t-Bu O 107- 0.85 100% 410 FAB B10,
 _Q NHMe 110 EtOAc (M+H)+ B4bq
 O-< N C2b
 105 t-Bu O 0.75 100% 396 HPLC B10,
 NH2 EtOAc (M+H)+ / ES- B02
 _Q - MS C2b
 O-< N
 106 t-Bu O 132- B3d
 142 135 step 2,
 C3a
 107 t-Bu 0.45 100% 369 FAB C2b
 EtOAc (M+H)+
 108 t-Bu 0.60 100% 365 FAB C2b
 EtOAc (M+H)+
 109 t-Bu O 0.55 40% 410 FAB B3bj
]=O EtOAc (M+H)+ C2bq D2
 me 60% Step 1,
 hexane D8
 110 t-Bu 176- B7. C2a
 N 178
 &2 CH2
 III i-Bu __/F]\ 195- 0.30 25% 397 FAB C2b
 aNO2 197 EtOAc (M+)
 75%
 hexane
 112 t-Bu N 179- B3b2
 182 C2a
 t-Bu Me 78- 0.25 10% 379 EI We,
 82
 EtOAc (M+) Ob
 90%
 Me CH2CI2
 114 t-Bu H2 203- 0.35 10% 340 FAB B89
 206 MeOH (M+H)+ B2bq
 0.5% C2b
 AcOH
 89.5%
 EtOAc
 115 t-Bu H 189- 0.20 30% 351 FAB C2b
 191
 EtOAc (M+H)+
 70%
 hexane
 116 t-Bu F 0.60 5% 404 FAB B3b
 acetone (M+H)+ step 1,2,
 95% ClD
 CH2CI2

117 t-Bu 0 234 0.30 5% 396 FAB B3a
 OH dec MeOH/ (M+H)+ Step 2,
 0 0.5% C2b
 AcOH
 94.5%
 CH202
 118 t-Bu 0 135-
 \---/]D 138
 119 t-Bu --Q 0 0.13 5% 486 FAB B3b
 acetone (M+H)+ step 1,2,
 Cl 95% Cld
 CH202
 121 t-Bu 177- 0.20 30% 351 FAB B7] B19
 -Q 178 EtOAc / (M+H)+ C2b
 H 2 C 70%
 I hexane
 122 t-Bu 0 - P] \-Jj 0.40 25% 366 FAB B3a,
 EtOAc / (M+H)+ C2b
 Me 75%
 hexane
 123 t-Bu 0 Me 150- 0.45 25% 380 FAB B3a,
 158 EtOAc / (M+H)+ C2b
 Me 75%
 hexane
 124 t-Bu 0 Cl 118- 0.50 25% 420 FAB B3a
 122 EtOAc / (M+H)+ Step I
 Cl 75% B3b
 hexane Step 2,
 C2b
 125 t-Bu -ao-Q 176- 0.55 25% 366 FAB B3a,
 182 EtOAc / (M+H)+ C2b
 Me 75%
 hexane
 126 t-Bu 176- 0.16 5% 386 FAB C2b
 177 MeOH / (M+H)+
 95%
 CH202
 Table 2. 3-Substituted isoxazolyl Ureas
 R'
 ,]Yj 0
 N I)] R2
 0 N N'
 H H
 mp TLC Solvent Mass Synth.

Ex. R1 R2 ('C) Rr System Source Method
 IN
 137 Me 0--aMe 169- 0.25 5% 324 FAB Clb
 170 acetone / (M+H)+
 95%
 CH2CI2
 138 i-Pr --&O-aMe 166- 0.54 50% 352 FAB Clb
 170 EtOAc (M+H)+
 50% pet
 ether
 139 i-Pr Cl Cl 148- 0.40 5% 313 El Clb
 149 acetone / (M+)
 95%
 CH2C12
 i-Pr H2 272 0.21 5% 337 FAB A2, C3a

```

--a CL C\N dec MeOH (M+H)+
95%
CHC13
141 i-Pr 0.25 5% 355 FAB A2]
_Q MeOH (M+H)+ B4a,
S - ]\:N 95% C3a
CHC13 I
142 i-Pr OMe 0.14 30% 368 FAB A21
EtOAc (M+H)+ B3a,
70% pet C3a
ether
143 i-Pr -a 0 - C\N 75- 0.22 5% 339 FAB A2, C3a
77 MeOH (M+H)+
dec 95%
1 CH202
144 i-Pr -&S- C\N 112- 0.29 5% 355 FAB A21
117 MeOH (M+H)+ B4a,
95% C3a
CH202
145 Cl Cl 171 0.33 5% 326 FAB Clb
acetone (M+H)+
95%
CH2Cl2
146 0 -<\:N 351 HPLC C8
(M+H) / ES-
+ Ms
147 0.03 50% 401 FAB C8
0 -N
EtOAc (M+H)
50% +
hexane
148 0 159- 0.22 5% 325 HPLC C4a
160 EtOAc/ (M+H) ES-
95% + Ms
hexane
149 190- 0.38 50% 350 FAB Clb
191 EtOAc (M+H)+
Me 50% pet
ether
150 Me 175- 0.43 50% 364 FAB Clb
4> 178 EtOAc (M+H)+
Me 50% pet
ether
151 n-Bu Cl Cl 133 0.37 5% 328 FAB Clb
acetone / (M+H)+
95%
CH202
152 t-Bu --&O--aMe 165 0.34 40% 366 FAB Clb
dec EtOAc (M+H)+
60% pet
ether
153 t-Bu Br 188- 0.82 5% 338 FAB Clb
189 acetone (M+H)+
95%
CH2CI2
154 t-Bu 182- 352 FAB
184 (M+H)+
t-Bu Ci 0.65 5% 294 FAB C2a
MeOH (M+H)+
95%

```

CH202
 156 t-Bu CF3 0.25 3% 328 FAB C2a
 MeOH (M+H)+
 97%
 CH202
 157 t-Bu Ci Ci 0.57 3% 328 FAB C2a
 MeOH (M+H)+
 97%
 CH2CI2
 158 t-Bu 0.60 5% 274 FAB C2a
 --Me
 MeOH (M+H)+
 95%
 CH2CI2
 159 t-Bu --&S- C\N 0.21 5% 369 FAB 134a,
 MeOH (M+H)+ C2a
 95%
 ClI2CI2
 160 t-Bu --/F]\S-a0l`r-n 0.52 50% 426 FAB B5, C4a
 EtOAc / (M+H)+
 50%
 hexane
 161 t-Bu --&O--&OBn 0.36 40% 458 FAB 133a,
 EtOAc / (M+H)+ C2b
 60%
 hexane
 162 t-Bu 213 0.05 5% 369 FAB C3a
 dec acetone / (M+H)+
 S- C\N 95%
 1 CH2C12
 163 t-Bu --& 0 - C\N 210 0.05 5% 353 FAB C3a
 dec acetone / (M+H)+
 95%
 CH202
 164 t-Bu 174- 0.25 5% 382 FAB C3a
 O-aOMe
 175 acetone / (M+H)+
 95%
 CH202
 165 t-Bu 90- 0.16 5% 409 FAB C2a
 N 92 acetone / (M+H)+
 0--], 1 95%
 S:04 CH2C12
 166 t-Bu N 221 0.14 5% 409 FAB C2a
 0--\0] 10
 s , 1]0 dec acetone (M+H)+
 95%
 CI-I2C12
 167 t-Bu H 182 0.28 40% 380 El A2, C3a
 -F\]-N OMe EtOAc (M+)
 60%
 hexane
 168 t-Bu N 196- 0.17 5% 368 FAB A21
 -IN
 0 -]\]/ OMe
 198 MeOH (M+H)+ B314
 N 95% C3a
 I I CH2C12
 t.-Bu 0-&OMe 204- 0.27 50% 383 FAB A2]
 -&N 206 EtOAc (M+H)+ B3a,

50% pet C3a
 ether
 170 t-Bu
 ---/ \ \-H2 179- 351 FAB A2, C3a
 --\=/-C-]\ N 180
 (M+H)+
 171 t-Bu 0.33 50% 414 EI A21
 -&s--&SMe EtOAc (M+) B4a,
 N
 50% pet C3a
 ether
 172 t-Bu \N 0-&SMe 188- 0.49 50% 399 HPLC A29
 189 EtOAc (M+H)+ ES- B4a,
 N
 50% pet Ms C3a
 ether
 173 t-Bu 0
 179. 0.14 5% 395 FAB A25
 Me 180 MeOH (M+H)+ B4a,
 95% C3a
 CH2Cl2
 174 t-Bu 0-&F 118- 0.19 5% 387 FAB A29
 121 MeOH (M+H)+ B4a,
 N
 95% C3a
 CH2Cl2
 175 t-Bu 0 N 197- 0.08 10% 353 FAB All
 199 acetone (M+H)+ B3h,
 90% C3a
 CH2Cl2
 176 t-Bu 208- 0.17 5% 3 FT FAB Ob
 212 MeOH (M+H)+
 95%
 CH2Cl2
 177 t-Bu S--&OCF3 155- 0.57 10% 453 FAB Ob
 156 MeOH / (M+H)+
 CH2Cl2
 178 t-Bu \N 0-&SCF3 163- 0.21 5% 453 BPLC Ob
 165 MeOH (M+H)+ / ES-
 95% Ms
 CH2Cl2
 179 t-Bu 109- 0.17 5% 369 FAB Ob
 112 MeOH (M+H)+
 95%
 CH2Cl2
 180 t-Bu N02 199- 0.60 5% Ob
 202 MeOH
 I -&-O I CH202
 181 t-Bu 160- 0.58 50% 336 Cl Ob
 162 EtOAc (M+)
 50% pet
 ether
 182 t-Bu
 --// \ S-&OMe 0.18 50% Ob
 \c4- EtOAc
 50% pet
 ther
 183 t-Bu 180 Ob
 / \N O-ame
 -CY

N
 184 t-Bu 0 214- Ob
 -& 217
 N Cl
 -C -
 N
 t-Bu N 0.13 50% 337 Ci Ob
 EtOAc (M+H)
 50% +
 hexane
 186 t-Bu 154- 0.51 50% 336 FAB Ob
 156 EtOAc (M+H)
 50% pet +
 ether
 187 Me 154- 0.50 50% 365 El Cib
 -.]-Me -ao-o 155 EtOAc (M+)
 Et 50% pet
 ther
 188 Me 25- 0.05 5% 383 FAB Oa
 ---],Me 221 acetone (M+H)+
 Et
 S -<\\:N dec 95%
 1 CH202
 189 Me 137- 0.25 5% 396 FAB C3a
 ---\\,]-Me -a OMe 138 acetone (M+H)+
 Et 95%
 CH202
 190 Me Ci Ci 196- 0.58 5% 342 FAB Clb
 --]-Me 199 acetone / (M+H+)
 Et 95%
 CH202
 19.1 Me Me 0-&Me 160- 0.37 5% 380 FAB Clb
 -a 162 acetone / (M+H+)
 Et 95%
 CH202
 192 Me N 199- 0.33 70% 468 FAB A29
 --\\]-me --ao--/\\, S:010:] 200 EtOAc (M+)+ 133e,
 Et 30% pet Oa
 ether
 193 Me H 161- 0.28 40% 394 El A2, E3a
 --]-Me -aN-aOMe 162 EtOAc (M+)
 Et 60%
 hexane
 194 Me H2 0.18 5% 364 El A2, Oa
]- Me C -]\\]N MeOH (M+)
 Et 95%
 CHC13
 195 Me 90- 0.19 30% 232 El A2, C3a
 -\\]-Me -a 0 - C\\N 92 EtOAc (M+)
 Et 70% pet
 ether
 196 Me 180- 0.26 30% A21
 Me --ao-acl 181 EtOAc Ob
 Et 70% pet
 ether
 197 Me 63- 410 FAB A2]
 0-&OMe
 65 (M+H)+ 133a,
 Et Oa
 198 Me 84 0.16 5% 381 FAB A2, Oa


```

---]-Me --&O-<\:N MeOH / (M+H)+
Et 95%
CHC13
199 Me 189- 0.16 5% 397 BPLC A21
--]-Et -aS- C\N 192 MeOH / (M+H)+ El-MS B4a,
Et 95% Oa
CHC13
Me H A2, C3a
CLC 175. 0.16 5% 379 FAB
]-Et N 177 MeOH (M+H)+
Et 95%
CHC13
201 Me 189- 0.17 5% 397 FAB A29
Et 191 MeOH (M+H)+ B4a,
Et -Q
S -- C\N 95% C3a
CHC13
202 Me 67 0.41 5% A25
-],Et -aO--&Me MeOH Ob
Et 95%
CHC13
203 Me 123- 414 FAB A2, C3a
--]-Et --&o-&ci 125 (M+H)+
Et I I 1
204 Me 135- 0.33 5% A25
--I;rEt 137 MeOH Ob
Et 95%
CHC13
205 Me 178- 0.39 5% 366 FAB Clb
-)7 180 acetone (M+H)+
Me Me
95%
CH2C12
206 --]-Me --&O-aMe 200- 0.44 5% 380 FAB Clb
202 acetone (M+H)+
Me Me
95%
CH2C12
207 Cl Cl 150- 0.39 5% 342 FAB Clb
rme
Me Me 154 acetone / (M+H)+
95%
CH2O2
208 155- 0.38 50% 377 EI Clb
156 EtOAc (M+)
50% pet
ether
209 Ph --aO-&Me 0.33 5% 386 FAB Clb
acetone (M+H)+
95%
CH2O2
210 s --&S- C\N 190- 0.23 5% 395 FAB A22
191 MeOH (M+H)+ B4a,
95% C3a
CH2O2
211 0 -aS- C\N 0.18 5% 379 FAB A21
MeOH (M+H)+ Ob
95%
CHC13
Table 3. N'-Substituted tert-butyl pyrazolyI Ureas

```

0
 N%)] , R2
 N N
 H H
 mp TLC Solvent Mass Synth.

Ex. R1 R] (OC) Rr System Spec. Source Method
 212 H 0.27 50% 351 FAB Clc
 EtOAc / (M+H)+
 50%
 hexane
 213 H Cl Cl 0.59 50% 327 FAB Clc
 EtOAc / (M+H)+
 50%
 hexane
 214 H H2 0.30 60% 350 FAB C4a
 -a CL C\N acetone (M+H)+
 /40%
 Cl12Cl2
 215 H --&O-&Me 204 0.06 5% 364 El C3b
 acetone (M+)
 / 95%
 CH2Cl2
 216 H 110- 0.05 5% 408 FAB C3b
 N ill acetone (M+H)+
 95%
 S, ICH2Cl2
 217 H 0 - C\N 228- 0.24 10% 351 El C3a
 232 MeOH (M+)
 dec 90%
 CHCl3
 218 H Cl 182- 0.05 40% 327 FAB A53
 Cl 184 EtOAc (M+H)+ Cle
 60%
 hexane
 219 H 110- 326 El A51
 -O]-CF3 112 (M+) Cle
 220 H 0.07 5% 368 FAB 134a,
 MeOH / (M+H)+ C4a
 S- C\N 95%
 1 CHCl3
 221 H --O]S-- C\N 0.18 5% 364 El B4,
 MeOH / (M+) C4a
 95%
 CHCl3
 222 H 0 160- 408 FAB A59 B6,
 .fl] 0 161 (M+H)+ C3b
 HO CF3 NHMe isolated
 at TFA
 01 I salt
 H --aO--&OMe 381 FAB C2b
 L 1183] (M+H)+ I I
 Me 0.35 70% 382 FAB B4a,
 -&S- C\N acetone (M+H)+ C4a
 /30%
 CH2O2
 225 Me 0.46 70% 382 FAB C4a,
 acetone (M+H)+ B4a
 S- C\N /30%
 CH2Cl2

226 Me S]fs 0.47 100% 497 FAB B3c,
 S-41 EtOAc (M+H)+ C4a
 N-N 'Ph
 227 Me s 0.46 100% 464 FAB B3c,
 --]' I Ph EtOAc (M+H)+ C4a
 I N I 1
 228 Me S Ph 0.50 100% 540 FAB BR,
 0] (Ph
]\ EtOAc (M+H)+ C4a
 229 Me CF3 0.52 100% 506 FAB BR,
 N:O,
 I EtOAc (M+H)+ C4a
 s
 230 Me CF3 0.51 100% 509 FAB BR,
 -]] 0-&Ph EtOAc (M+H)+ C4a
 231 Me 0-&Bu-t 0.75 100% 421 FAB BR,
 -a EtOAc (M+H)+ C4a
 232 Me O-aSCF3 0.50 100% 465 FAB BR,
 EtOAc (M+H)+ C4a
 233 Me Ph 0.50 100% 349 FAB C4a
 EtOAc (M+H)+
 234 Me 0.09 50% 381 FAB C4a
 EtOAc (M+H)+
 50%
 hexane
 235 Me 0-aOBn 0.60 100% 471 FAB B21
 I IEtOAc (M+H)+ C4a
 236 Me OH 0.61 100% 397 FAB BR,
 -&S-a I EtOAc (M+H)+ C4a
 237 Me S--&OPr-n 0.42 100% 439 FAB B5]
 EtOAc (M+H)+ C4a
 238 Me S--&OBu-n 0.25 50% 453 FAB B5]
 EtOAc (M+H)+ C4a
 50%
 hexane
 239 Me H2 0.65 100% 462 FAB B69
 NH EtOAc (M+H)+ C4a
]=O
 i-Bu
 240 Me H2 0.67 100% 478 FAB B6]
 C NH EtOAc (M+H)+ C4a
]=o
 t-BuO
 241 Me H2 0.50 1100%c 1378 FAB C4a
 I I -0] - CL&-2 EtOA (M+H)+ I I I
 Me H 0.30 100% 557 FAB C4a
 NH EtOAc (M+H)+
]=O
 RNe
 243 Me H2 0.33 100% 420 FAB C4a,
 C NH EtOAc (M+H)+ D3
 /)=o
 Me
 244 Me H2 0.60 10% 478 FAB C4a,
 NH water (M+H)+ D3
 0 90%
 H02C CH3CN
 245 Me -4]VO-&]-/, NH 0.28 100% 559 FAB C4a
]=O EtOAc (M+H)+
 HNe

246 Me -//]\\\ -O NH 0.40 100% 436 FAB C4a,
 &-/N/]=O EtOAc (M+H)+ D3
 Et/
 247 Me NH 0.46 50% 422 FAB C4a,
]=O acetone (M+H)+ D3
 Me 150%
 CH2CI2
 248 Me 0.50 100% 464 FAB C4a,
 0 - NH EtOAc (M+H)+ D3
]=O
 i-Bu
 Me HL& 0.55 100% 434 FAB C4a,
 249 2] -/
 C NH EtOAc (M+H)+ D3
 Et I 1
 250 Me 0-aNH2 0.52 100% 380 FAB C4a
 -a EtOAc (M+H)+
 251 Me FAB C4a
 \\\ -O-C\N 0.25 60% 366
 acetone (M+H)+
 /40%
 CH2CI2
 252 Me 0.52 100% 452 FAB C4a,
 -aO-<\a/N, NH EtOAc (M+H)+ D3
]=O
 EtO
 253 Me 0.52 100% 466 FAB C4a,
 -aO- NH EtOAc (M+H)+ D3
]=O
 i-pro
 254 Me H2] - 0.34 60% 396 FAB C4a
 -&S-C-]\N acetone (M+H)+
 /40%
 CH2CI2
 255 Me H2 0.36 60% 396 FAB C4a
 --ac-S- C\N acetone (M+H)+
 /40%
 CH2O2
 256 Me 0-0 147- 365 FAB Clc
 I -]a 149 (M+H)+
 257 Me Cl Cl 173- 341 FAB Clc
 175 (M+H)+
 Me CF3 185- 341 BIPLC / C I c
 187 (M+H)+ ES-MS
 259 Me Br 195- 429 FAB Clc
 197 (M+H)+
 Br
 260 Me -.&CO2Bu-n 0.25 50% 373 FAB Clc
 EtOAc / (M+H)+
 50%
 hexane
 261 Me H2 161- 0.15 4% 364 FAB C2b
 C I C\N 162 MeOH / (M+H)+
 96%
 CH2CI2
 262 Me '-&O-&Me 228 379 FAB C2b
 dec (M+H)+
 263 Me
 0.30 5% 422 FAB C2b
 MeOH / (M+H)+

N]
 0__] - 95%
 SAJ CH2CI2
 264 Me CF3 0.32 70% 450 FAB Wb]
 -]S- C\N acetone (M+H)+ C4a
 /30%
 1 CH202
 265 Me H2H2 0.15 40% 379 FAB B1] B2]
 C - C acetone (M+H)+ Oa
 N 60%
 CH202
 266 Me H2 0.10 20% 380 FAB C4a
 --&O-CL C\N acetone (M+H)+
 / 80%
 CH202
 267 Me H 0.20 80% 365 FAB Oa
 -F\]\-N- C\N
 EtOAc / (M+H)+
 20%
 hexane
 268 Me H2H2 r---\ 0.48 30% 378 FAB B11
 acetone (M+H)+ C3a
 /70%
 CH2CI2
 269 -CH2CF3 0.22 30% 433 FAB A3]
 EtOAc (M+H)+ Clb
 70%
 hexane
 270 -CH2CF3 Cl 1 0.38 30% 409 FAB A3]
 EtOAc (M+H)+ Clb
 ./70%
 hexane
 271 -(CH2)2CN Cl Cl 0.53 70% 380 BPLC / A3,
 EtOAc (M+) ES-MS Clb
 30%
 hexane
 272 -(CH2)2CN 0.37 70% 404 BIPLC / A39
 EtOAc (M+H)+ ES-MS Cib
 30%
 hexane
 -(CH2)2OH Cl Cl 0.15 60% 371 FAB A32
 EtOAc / (M+H)+ CM
 40% D4
 hexane
 274 --O 2 0.49 40% 432 FAB A31
 C' C\N acetone (M+H)+ C4a
 / 60%
 CH2CI2
 275 -CH2CO2Et Cl Cl 0.44 50% 413 FAB A3]
 EtOAc / (M+H)+ Clb
 50%
 hexane
 276 Cl Cl 0.59 60% 398 FAB A3]
 O=< CH2 acetone (M+H)+ Clb?
 NHMe /40%. D5a
 CH202
 277 0 Me-NH 159- 508 FAB A59 B62
 0 0 161 (M+H)+ C2b
 t-B']
 Table 4. 5-Substituted thiadiazolyl Ureas

RI
]-S O
 N
 'N N A W R2
 H H
 MP TLC Solvent Mass Synth.

Ex. R1 R] (OC) Rr System Spec. Source Method
 278 t-Bu Me 243- 355 HPLC / Cic
 JD 244 (M+H)+ ES-MS
 279 t-Bu --&O--]&Me 0.30 5% 383 FAB Clb
 acetone (M+H)+
 / 95%
 C11202
 280 t-Bu 0- C\N 0.26 5% 370 FAB C3a
 MeOH / (M+H)+
 95%
 C11202
 281 t-Bu 386 FAB 134a,
 (M+H)+ C3a
 S- C\N I 1
 282 t-Bu --&O-&OMe 0.37 5% 399 FAB B3a,
 MeOH / (M+H)+ C3a
 95%
 CH2C12
 Table 5. 5-Substituted thienyl Ureas

RI
 0
 S])] , R2
 N N
 H H
 2 mp TLC Solvent Mass Synth.

Ex. R1 R (OC) System Spec. Source Method
 283 t-Bu 144- 0.68 5% A09
 145 acetone Cla
 /95%
 C11202
 284 t-Bu 0 N 0.28 50% 368 BPLC / A4a
 Et2O (M+H)+ ES-MS
 50% pet
 ether
 285 t-Bu e 57 381 FAB A4a
 -ao-&M (M+H)+
 286 t-Bu H2 0.15 50% 365 El A4a
 --a C L C\N EtOAc / (M+)
 50% pet
 ether
 287 i-Bu --&O-&OH 0.44 50% 383 FAB A4a
 EtOAc / (M+H)+
 50% pet
 ether
 t-Bu S- C\N 0.36 50% 384 FAB A4a
 EtOAc / (M+H)+
 50% pet
 ether
 289 t-Bu Cl Cl 169- 0.57 20% 343 FAB A4c,
 170 EtOAc / (M+H)+ ClD
 80%
 hexane

290 t-Bu 155- 0.40 20% 411 FAB D2
 156 EtOAc / (M+H)+
 80%
 hexane
 291 t-Bu O-aopr-i 165- 0.40 20% 425 FAB D2
 166 EtOAc (M+H)+
 80%
 hexane
 292 t-Bu _/[]\]O-aOBu-i 188- 0.45 20% 439 FAB D2
 189 EtOAc (M+H)+
 80%
 hexane
 293 t-Bu 0 <\:N 0.13 50% 368 FAB A4c,
 EtOAc (M+H)+ C4c
 50%
 hexane
 294 t-Bu --&O-aOMe 0.26 30% 397 BPLC / A4c,
 Et2O (M+H)+ ES-MS CId
 70% pet
 ether
 295 t-Bu Me 0.52 30% 381 HPLC / A4a
 Et2O (M+H)+ ES-MS
 70% pet
 ether
 Table 5. Additional Ureas
 mp TLC Solvent Mass Synth.

Ex. R' (OC) Rr System Spec. Source Method
 296 161- 0.71 20% 367 FAB DI
 163 EtOAc (M+H)+
 0 80%
 N]k NgC1 hexane
 Br H H C1
 297 162- 0.52 30% 365 FAB A89 CId
 0 164 EtOAc (M+H)
 N 0 70% +
 N)] Nia Me hexane
 H H
 298 Br 0.67 5% 388 FAB Clb
 acetone (M+H)+
 /95%
 CH2Cl2
 N 0 f
 N 'J] N
 H H
 C1 0.72 90% 380 BPLC MS
 EtOAc / (M+H) ES
 0 10% + B0]
 HNI N hexane C4a
 I
 N N N
 HH
 300 170- 0.40 5% 328 FAB CM
 172 acetone (M+H)+
 / 95%
 N] CH202
 0 NN C1
 HH C1
 301 179- 362 BPLC C5
 181 (M+H)+ ES-MS

N 0
 N)]N
 H
 302 155- 0.44 5% 380 FAB Clb
 157 acetone (M+H+)
 / 95%
 0 ON CH2Cl2
 NN']]
 302 0.55 90% 443 FAB B101
 0 EtOAc (M+H)+ B4b,
 0 1 10% C2b
]U' zz]' N hexane
 NNj:] (
 HH
 NHMe
 303 0 OEt 230 377 HPLC / C5
 0 dec (M+H)+ ES-MS
 NANjcc:p
 H
 BIOLOGICAL EXAMPLES
 P38 Kinase AssM.

The in vitro inhibitory properties of compounds were determined using a p38 kinase inhibition assay. P38 activity was detected using an in vitro kinase assay run in 96-well microtiter plates. Recombinant human p38 (0.5 Vg/mL) was mixed with substrate (myelin basic protein, 5 Vg/mL) in kinase buffer (25 mM Hepes, 20 mM M902 and 150 mM NaCl) and compound. One Vci/well of 33 P-labeled ATP (10 VW was added to a final volume of 100 VL. The reaction was run at 32 °C for 30 min. and stopped with a 1M HCl solution. The amount of radioactivity incorporated into the substrate was determined by trapping the labeled substrate onto negatively charged glass fiber filter paper using a 1% phosphoric acid solution and read with a scintillation counter.

Negative controls include substrate plus ATP alone.

All compounds exemplified displayed p38 IC50S of between 1 nM and 10 μM.

LPS Induced TNF Production in Mice.

The in vivo inhibitory properties of selected compounds were determined using a murine LPS induced TNFα production in vivo model. BALB/c mice (Charles River Breeding Laboratories; Kingston, NY) in groups of ten were treated with either vehicle or compound by the route noted. After one hour, endotoxin (E. coli lipopolysaccharide (LPS) 100 μg was administered intraperitoneally (i.p.). After 90 min, animals were euthanized by carbon dioxide asphyxiation and plasma was obtained from individual animals by cardiac puncture into heparinized tubes. The samples were clarified by centrifugation at 12,500 x g for 5 min at 4 °C. The supernatants were decanted to new tubes, which were stored as needed at -20 °C.

TNF α levels in sera were measured using a commercial murine TNF ELISA kit (Genzyme).

The preceding examples can be repeated with similar success by substituting the generically of specifically described reactants and/or operating conditions of this invention for those used in the preceding examples. From the foregoing discussion, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

CLAIMS (ENGLISH) What is claimed is:

1. A method for the treatment of a disease mediated by p38 other than cancer, comprising administering a compound of formula I

0
wherein B is a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein if B is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and X_n, wherein n is 0-3 and each X is independently selected from the group consisting of -CN, -CO₂R, -C(O)NRR⁵, -C(O)R, -NO₂, -OR'^q - SR⁵, - NRV, -NR'C(O)OR, -NR'C(O)R⁵, CI-Clo alkyl, C2-CIO alkenyl, CI-Clo alkoxy, C3-CIO cycloalkyl, C6-CI₄ aryl, C7-C2₄ alkaryl, C3-CI₃ heteroaryl, C4-C2₃ alkheteroaryl, substituted CI-CI(alkyl, substituted C2-Clo alkenyl, substituted CI-Clo alkoxy, substituted C3-CIO cycloalkyl, substituted C4-C2₃ alkheteroaryl and -Y-Ar; wherein if X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of -4CN, -COA₅i -C(O)R', -C(O)NIR, -OR⁵, -SR, -NRR, -NO₂, -NRC(O)R, -NRC(O)OR and halogen up to per-halosubstitution; wherein R⁵ and W are independently selected from H, CI-CIO alkyl, C2-CIO alkoyl, C3-CIO cycloalkyl, C6-CI₄ aryl, C3-CI₃ heteroaryl, C7-C2₄ alkaryl, C4-C2₃ 3o alkheteroaryl, up to per-halosubstituted CI-Clo alkyl, up to per-halosubstituted C3-CIO cycloalkyl, up to per-halosubstituted C2-CIO alkenyl, up to per-halosubstituted C6-CI₄ aryl and up to per-halosubstituted C3-CI₃ heteroaryl, wherein Y is , -S-, -N(R)-g - (CH₂)-m₂ -C(O)-2 -CH(OH)-j - (CH₂)m₀-i - (CH₂)m_S-] - (CH₂)m_N(R)-i -O(CH₂)m-i]CjjXa. NR⁵C(O)NR⁵ R⁵'_, _NR⁵C(O)_ , -C(O)NR'-, -CXa₂-, -S-(CH₂), , , - and -N(R)(CH₂)m-] m = 1-3, and V is halogen; and Ar is a 5-10 member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z, , , , wherein n₁ is 0 to 3 and each Z is independently selected from the group consisting of --CN, -CO₂R, -C(O)NWR, -C(O)- NW₉ -NO₂ =07 -OR'^q - SR']

NR'R. -C(O)R', -SO₂R, -SO₂NR'R, -NR'C(O)OR₅'. -NR'C(O)W', CI-Clo alkyl
 CI-Clo alkoxy, C3-CIO cycloalkyl, C6-CI₄ aryl, C3-CI₃ heteroaryl, C7-C24
 alkaryl, C4-
 C23 alkheteroaryl, substituted CI-CIO alkyl, substituted C3-CIO cycloalkyl,
 substituted
 C7-C24 alkaryl. and substituted C4-C23 alkheteroaryl;
 wherein if Z is a substituted group, it is substituted by the one or more
 substituents independently selected from the group consisting of -CN, -CO₂R,
 5'_C(O)NRIRI', =O, -OR'] -SR', -NO₂. -NRR. -NRC(O) ']
 -C(O)R] W
 -NR₅C(O)OR, CI-Clo alkyl, CI-Clo alkoxy, C3-CIO cycloalkyl, C-Clo heteroaryl,
 C6-
 C1₄ arYI, C4-C24 alkheteroaryl and C7-C24 alkaryl.
 A is a heteroaryl moiety selected from the group consisting of
 R R' Ra R I
 N Rc N Rc NJN'%%'S S W:kS
 I I I ==
 R N IL) I N
 R' R' R R
 1
 JNl.,0 N N N, N N
 N 11
 I =:= N
 N
 R R'
 R R
 0 S 0
 1
 N and S
 Rb Rb
 wherein
 RI is selected from the group consisting of halogen, C3-Clo alkyl, C3-CIO
 cycloalkyl, C1-CI₃ heteroaryl, C6-14 aryl, C7-24 alkaryl, up to
 per-halosubstituted Cj-
 CIO alkyl, up to per-halosubstituted C3-CIO cycloalkyl, up to
 per-halosubstituted CI-CI₃
 heteroaryl, up to per-halosubstituted C6-14 aryl, and up to
 per-halosubstituted C7-24
 lo alkaryl;
 3'
 R₂ is selected from the group consisting of H. -C(O)R], -CO₂R], -C(O)NWR
 CI-CIO alkyl. C3-CIO cycloalkyl, C7-C24 alkaryl, C4-C23 alkheteroaryl,
 substituted Cj-
 CIO alkyl, substituted C3-CIO cycloalkyl, substituted C7-C24 alkaryl and
 substituted C4-
 C23 alkheteroaryl,
 where W is a substituted group, it is substituted by one or more substituents
 independently selected from the group consisting of -CN, - CO₂R], -C(O)-WR₃',
 'NO₂, -OR], -SR], and-halogen up to per-halosubstitution,
 wherein R₃ and R₃' are independently selected from the group consisting of
 H,
 -OW, -SW₉ -NWW'] -C(O)W, -CO₂R₄, -C(O)NleW'q CI-CIO alkyl, C3-CIO CYC1oalkyl,
 C6-CI₄ arYl, C3-CI₃ heteroaryl, C7-C24 alkaryl, C4-C23 alkheteroaryl, up to
 per-
 halosubstituted CI-CIO alkyl, up to per-halosubstituted C3-CIO cycloalkyl, up
 to per-
 halosubstituted C6-CI₄ aryl. and up to per-halosubstituted C3-C,3 heteroaryl;
 and
 wherein R] and R]'are independently selected from the group consisting of H,
 CI-Clo alkyl, C3-CIO cycloalkyl, C6-CI₄ aryl, C3-CI₃ heteroaryl.; C7-C24

alkaryl, C4-C23

aMeteroaryl, up to per-halosubstituted CI-Clo alkyl, up to

per-halosubstituted C3-CIO

cycloalkyl, up to per-halosubstituted C6-CI4 aryl and up to

per-halosubstituted C3-CI3

heteroaryl,

V is CI-CIO alkyl, C3-CIO cycloalkyl, up to per-halosubstituted CI-CIO alkyl

io . and up to per-halosubstituted C3-CIO cycloalkyl; and

R] is hydrogen or halogen,

R' is hydrogen, halogen, CI-Clo alkyl, up to per-halosubstituted CI-CIO alkyl

or combines with R' and the ring carbon atoms to which R1 and W are bound to

form

a 5- or 6-membered cycloalkyl, aryl or hetaryl ring with 0-2 members selected

from

0.) N and S.

2 A method as in claim 1, wherein B is up to a tricyclic aromatic ring

structure selected from the group consisting of

Xn Xn

0 0

R5 R5

N N

and

which is substituted or unsubstituted by halogen, up to per-halosubstitution,

and

wherein n = 0-3 and each X - is independently selected from the group

consisting of -CN, -CO2R, -C(O)NWR, -C(O)R', -NO2, -OR'q - SR'] - i]R5R5'9

-NR'C(O)QR 5'q -NWC(O)W'] Ci-Clo alkyl, C2-lo-alkenyl, C1 alkoxy, C3-CIO

cycloalkyl, C6-CI4 aryl, C7-C24 alkaryl, C3-CI3 heteroaryl, C4-C23

aRdieteroaryl, and

substituted CI-Clo alkyl, substituted C2 alkenyl, substituted CI alkoxy,

substituted C3-CIO cycloalkyl, substituted C4-C23 alkheteroaryl and -Y-Ar;

wherein if X is a substituted group, it is substituted by one or more

substituents independently selected from the group consisting of -CN, -CO2R'q

-C(O)R', -C(O)NRR5', -OR, -SR, -NRR, NO2, -NRC(O)R, -NRC(O)OR and

io halogen up to per-halosubstitution;

wherein R5 and R5' are independently selected from H, C I -C 1 o alkyl, C2.1

0-

alkenyl, C3-CIO cycloalkryl, C6-CI4 aryl, C3-CI3 heteroaryl, C7-C24 alkaryl,

C4-C23

alkheteroaryl, up to per-halosubstituted CI-Clo alkyl, up to

per-halosubstituted C2

alkenyl, up to per-halosubstituted C3-CIO cycloalkyl, up to

per-halosubstituted C6-CJ4

aryl. and up to per-halosubstituted C3-CI3 heteroaryl,

wherein Y is - O-, -S-, -N(W)-] -(CH2)-mi -C(O)-9 -CH(OH)-q -(CH2)m&]

_NR5C(O)NR5R5', _NR5C(O)_ , _C(O)NRI_ , -(CH2)MS-1 -(CH2)mN(R)-] -O(CH2)m-]

_CHXa. _CXa 2-] -S-(CH2)m- and -N(R5)(CH2)m-i

m = 1-3, and Xa is halogen; and

Ar is a 5-10 member aromatic structure containing 0-4 members of the group

consisting of nitrogen, oxygen and sulfur which is unsubstituted or

substituted by

halogen up to per-halo and optionally substituted by Znj, wherein nI is 0 to

3 and each

Z is independently selected from the group consisting of -CN, -CO2R, -C(O)R,

--Oq

_SO2R'q _SO2NjeRI'. _C(O)NR5R5', 'C(O)R59 'NO2. -OR, -SR, -NRR,

-NRC(O)OR. -NRC(O)R5', CI-Clo alkyl, CI-Clo alkoxy, C3-CIO cycloalkyl, C6-CI4

aryl, C3-CI3 heteroaryl, C7-C24 alkaryl, C4-C23 alkheteroaryl, substituted

CI-Clo alkylq

substituted C3-C10 cycloalkyl, substituted C7-C24 alkaryl. and substituted C4-C23 alkheteroaryl; wherein if Z is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of -CN, -CO₂W, -C(O)NRR, =O, -OR, -SR, -NO₂, -NRR₅' , -NRC(O)R, -NRC(O)OR, C1-C10 alkyl, C1-C10 alkoxy, C3-C10 cycloalkyl, C-Clo heteroaryl, C6-C14 aryl, C4-C24

alkheteroaryl and C7-C24 alkaryl.

, A method of claim 1, wherein B is

X

n

(V) Qts]Zn1

wherein Y is selected from the group consisting of , -S-, -CH₂-, -SCH₂-, -CH₂S', -CH(OH)-, -C(O)-, -CXa₂, -CXaH-, -CH₂O- and -OCH₂-, where X' is halogen,

Q is a six member aromatic structure containing 0-2 nitrogen, substituted or unsubstituted by halogen, up to per-halosubstitution;

Q1 is a mono- or bicyclic aromatic structure of 3 to 10 carbon atoms and 0-4 members of the group consisting of N, O and S, unsubstituted or unsubstituted by

halogen up to per-halosubstitution, and

X, Z, n and n1 are as defined in claim 1 and s is 0 or 1.

4 A method as in claim 3, wherein

Q is phenyl. or pyridinyl, substituted or unsubstituted by halogen, up to per-halosubstitution,

Q1 is selected from the group consisting of phenyl, pyridinyl, naphthyl, pyrimidinyl, quinoline, isoquinoline, imidazole and benzothiazolyl, substituted or

unsubstituted by halogen, up to per-halo substitution, or -Y-Q1 is phthalimidinyl

substituted or unsubstituted by halogen up to per-halo substitution, and

Z and X are independently selected from the group consisting of -R₆, -OR] 2o and -NHR₇, wherein R₆ is hydrogen, C1-Clo-alkyl or C3-Clo-cycloalkyl and R₇ is

selected from the group consisting of hydrogen, C3-Clo-alkyl,

C3-C6-cycloalkyl and

C6-C10-aryl, wherein R₆ and R₇ can be substituted by halogen or up to per-halosubstitution.

5 A method as in claim 1, comprising administering a compound of the formula

R'

N

I 0

N I I

R NH-C-NH-B

wherein R' and R₂ and B are as defined in claim 1.

6 A method as in claim 5, wherein B is 2,3-dichlorophenyl or of the formula

X

n

U - (Y__ Q'ts-Zn 1

wherein Q is phenyl, Q1 is phenyl or pyridinyl, Y is , -S-, -CH₂- or -SCH₂, X is

CF₃, and Z is -OH, -Cl or NHC(O)-C,,H_{2p+1}, where p = 2-4, s = 0 or 1, n = 0 and n1

0 or 1.

7 A method as in claim I comprising administering a compound selected from the group consisting of-

N-(3-tert-Butyl pyrazolyl)-N'-(4-(2,3-dichlorophenyl)urea);
 N-(3-tert-Butyl pyrazolyl)-N]-(3-(4-pyridinyl)thiophenyl)urea;
 N-(3-tert-Butyl pyrazolyl)-N]-(4-(4-pyridinyl)methylphenyl)urea;
 N-(3-tert-Butyl pyrazolyl)-N-(4-(4-pyridinyl)oxyphenyl)urea;
 N-(3-tert-Butyl pyrazolyl)-N'-(4-(4-pyridinyl)thiophenyl)urea;
 N-(3-tert-Butyl pyrazolyl)-N'-(4-(4-pyridinyl)methylphenyl)urea;
 N-(1-Methyl tert-butyl pyrazolyl)-N'-(2,3-dichlorophenyl)urea;
 N-(1-Methyl tert-butyl pyrazolyl)-N'-(4-(4-hydroxyphenyl)thiophenyl)urea;
 N-(1-Methyl tert-butyl pyrazolyl)-N'-(4-(4-ethylaminocarbonylphenyl)oxyphenyl)urea;
 N-(1-Methyl tert-butyl pyrazolyl)-N]-(4-(4-isobutylaminocarbonylphenyl)thiophenyl)urea;
 N-(1-Methyl tert-butyl pyrazolyl)-N-(4-(4-pyridinyl)thiophenyl)urea;
 N-(1-Methyl tert-butyl pyrazolyl)-N'-(3-(4-pyridinyl)thiophenyl)urea;
 N-(1-Methyl tert-butyl pyrazolyl)-N]-(4-(4-pyridinyl)thio-(trifluoromethyl)phenyl)urea;
 N-(1-Methyl tert-butyl pyrazolyl)-N]-(4-(4-pyridinyl)oxyphenyl)urea;
 N-(1-Methyl tert-butyl pyrazolyl)-N]-(4-(4-pyridinyl)methylthio-phenyl)urea;
 N-(1-(2,2,2-Trifluoroethyl) tert-butyl pyrazolyl)-N]-(2,3-dichlorophenyl)urea;
 N-(1-(2-Hydroxyethyl) tert-butyl pyrazolyl)-N'-(2,3-dichlorophenyl)urea;
 N-(1-Ethoxycarbonylmethyl tert-butyl pyrazolyl)-N]-(2,3-dichlorophenyl)urea;
 N-(1-(2-Cyanoethyl) tert-butyl pyrazolyl)-N'-(2,3-dichlorophenyl)urea;
 N-(1-(3-Hydroxyphenyl)methyl tert-butyl pyrazolyl)-N'-(2,3-dichlorophenyl)urea;
 N-(1-Cyclohexyl tert-butyl pyrazolyl)-N]-(4-(4-pyridinyl)methylthio phenyl) urea;
 N-(1-methyl3-phenyl pyrazolyl)-N'-(3-(4-(2-methylcarbamoyl)-pyridyl)thiophenyl) urea;
 N-(1-methyl tert-butyl pyrazolyl)-N'-(4-(4-pyridyl)thiophenyl) urea;
 N-(1-methyl tert-butyl pyrazolyl)-N'-(3-(4-pyridyl)thiophenyl) urea;
 N-(1-methyl tert-butyl pyrazolyl)-N]-(3-trifluoromethyl (4-pyridylthio)phenyl) urea;
 N-(3-tert-butyl pyrazolyl)-N'-(3-(4-pyridyl)oxyphenyl) urea;
 N-(3-tert-butyl pyrazolyl)-N'-(4-(4-pyridyl)oxyphenyl) urea;
 and pharmaceutically acceptable salts thereof

8 A method as in claim 5, wherein R' is t-butyl.

9 A method as in claim I comprising administering a compound of the formula

R

O O

N H - B

wherein R1 and B are as defined in claim 1.

. A method as in claim 9, wherein B is

X

n

(Y-- Q1s-Zn 1

wherein Q is phenyl, Q1 is phenyl or pyridinyl, Y is --O-, -S- or -CH2, X is CF3, Z is

OH] CH3, - O-CpH2p+1, wherein n = 2-6 or -C(O)-NH-CH3, S = 1, n = 0 or 1 and nI

0 or 1.

11 A method as in claim 1 comprising administering a compound selected from the group consisting of-

N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-hydroxyphenyl)oxyphenyl)urea;
 N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-isopropoxyphenyl)oxyphenyl)urea;
 N-(5-tert-Butyl isoxazolyl)-N-(4-(4-isobutoxyphenyl)oxyphenyl)urea;
 N-(5-tert-Butyl isoxazolyl)-N]-(4-(4-pentyloxyphenyl)oxyphenyl)urea;
 N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-methylaininocarbonylphenyl)-oxyphenyl)urea;
 N-(5-tert-Butyl isoxazolyl)-N'-(3-(4-pyridinyl)thiophenyl)urea;
 N-(5-tert-Butyl isoxazolyl)-N-(3-(4-pyridinyl)oxyphenyl)urea;
 N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-pyridinyl)oxyphenyl)urea;
 N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-pyridinyl)thiophenyl)urea;
 N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-pyridinyl)methylphenyl)urea;
 N-(5-tert-Butyl isoxazolyl)-N'-(4-(4-pyridinyl)thio (trifluoromethyl)-phenyl)urea;
 N-(5-tert-Butyl isoxazolyl)-N'-(3-(3-methyl pyridinyl)thiophenyl)urea;
 N-(5-tert-Butyl isoxazolyl)-N]-(3-(3-methyl pyridinyl)oxyphenyl)urea;
 N-(5-tert-Butyl isoxazolyl)-N'-(4-(3-methyl pyridinyl)oxyphenyl)urea;
 N-(5-tert-Butyl isoxazolyl)-N'-(4-(3-methyl pyridinyl)thiophenyl)urea;
 N-(5-tert-butyl isoxazolyl)-N-(4-(4-(2-methylcarbamoyle)pyridyl)-oxyphenyl)urea;
 N-(5-tert-butyl isoxazolyl)-N'-(3-(4-(2-methylcarbamoyle)-pyridyl)oxyphenyl)urea;
 N-(5-tert-butyl isoxazolyl)-N'-(4-(4-(2-carbamoyl)pyridyl)oxyphenyl)urea;
 N-(5-tert-butyl isoxazolyl)-N-(3-(4-(2-carbamoyl)pyridyl)oxyphenyl)urea;
 N-(5-tert-butyl isoxazolyl)-N]-(3-((4-pyridyl)fluoromethyl)phenyl)urea;
 N-(5-tert-butyl isoxazolyl)-N]-(3-((4-pyridyl)oxomethyl)phenyl)urea;
 and pharmaceutically acceptable salts thereof

12 A method as in claim 9, wherein R1 is t-Butyl.

13 A method as in claim I comprising administering a compound of the formula

R'

N 0

1 1 1

0 NH-C M-B

wherein R1 and B are as defined in claim 1.

14 A method as in claim 13, wherein B is 2,3-dichlorophenyl or of the formula

x

I n

Q - (Y__ Qt_Zn 1

wherein Q is phenyl, Q1 is phenyl, pyridinyl or benzothiazolyl, Y is , -S-, -CH2-

or -NH-, Z is Cl, -CH3 or -OCH3, s = 0 or 1, n = 0 and n1 = 0 or 1.

15 A method as in claim 13, wherein R1 is t-butyl.

16 A method as in claim 1 comprising administering a compound selected from the group consisting of :

N-(3-Isopropyl isoxazolyl)-N-(3-(4-pyridinyl)thiophenyl)urea;
 N-(3-tert-Butyl isoxazolyl)-N]-(2,3-dichlorophenyl)urea;
 N-(3-tert-Butyl isoxazolyl)-N'-(4-(4-methoxyphenyl)aminophenyl)urea;
 N-(3-tert-Butyl isoxazolyl)-N'-(4-(4-methoxyphenyl)oxyphenyl)urea;
 N-(3-tert-Butyl isoxazolyl)-N'-(4-(4-pyridinyl)oxyphenyl)urea;
 N-(3-tert-Butyl isoxazolyl)-N'-(4-(4-pyridinyl)thiophenyl)urea;

N-(3-tert-Butyl isoxazolyl)-N-(4-(4-pyridinyl)methylphenyl)urea;
 N-(3-(1,1-Diethylpropyl) isoxazolyl)-N-(4-(4-pyridinyl)methylphenyl)urea;
 N-(3-(1,1-Dimethylpropyl) isoxazolyl)-N-(3-(4-pyridinyl)thiophenyl)urea;
 N-(3-(1,1-Dimethylpropyl) isoxazolyl)-N-(4-(2-benzothiazolyl)-oxyphenyl)urea;
 N-(3-(1-Methyl-1-ethylpropyl) isoxazolyl)-N-(4-(4-pyridinyl)oxyphenyl)urea;
 N-(3-(1-Methyl-1-ethylpropyl) isoxazolyl)-N-(4-(4-pyridinyl)methylphenyl)urea;
 N-(3-cyclobutyl isoxazolyl)-N'-(4-(4-pyridyl)oxyphenyl) urea;
 N-(3-tert-butyl isoxazolyl)-N'-(4-(4-pyridyl)thiophenyl) urea;
 N-(3-(1-methyl-1-ethylpropyl) isoxazolyl)-N-(4-(4-pyridyl)oxyphenyl) urea;
 N-(3-tert-butyl isoxazolyl)-N'-(4-(4-pyridyl)methylphenyl) urea;
 N-(3-tert-butyl isoxazolyl)-N'-(4-(4-methoxyphenyl)aminophenyl) urea;
 and pharmaceutically acceptable salts thereof

17 A method as in claim 1 comprising administering a compound of the formula

R1

S 0

INH-C-NH-B

Rb

wherein R1, R] and B are as defined in claim 1.

. A method as in claim 17, wherein B is of the formula

X

n

Q']s-Zni

wherein Q is phenyl, Q1 is phenyl or pyridinyl, Y is or -S- or -CH2-, Z is OH,

CH3, Cl, -OC2H5 or -OC3H7, s = 0 or 1, n = 0 and n1 = 0 or 1.

19 A method as in claim 17, wherein R1 is t-butyl.

20 A method as in claim 17, wherein R] is hydrogen.

21 A method as in claim 1 comprising administering a compound selected from the group consisting of-

N-(2-Bromo tert-butyl thienyl)-N'-(4-methylphenyl)urea;
 N-(5-tert-Butyl thienyl)-N'-(2,3-dichlorophenyl)urea;
 N-(5-tert-Butyl thienyl)-N'-(4-(4-hydroxyphenyl)oxyphenyl)urea;
 N-(5-tert-Butyl thienyl)-N]-(4-(4-ethoxyphenyl)oxyphenyl)urea;
 N-(5-tert-Butyl thienyl)-N'-(4-(4-isopropoxyphenyl)oxyphenyl)urea;
 N-(5-tert-Butyl thienyl)-N'-(4-(3-pyridinyl)oxyphenyl)urea;
 N-(5-tert-Butyl thienyl)-N'-(4-(4-pyridinyl)oxyphenyl)urea;
 N-(5-tert-Butyl thienyl)-N'-(4-(4-pyridinyl)thiophenyl)urea;
 N-(5-tert-Butyl thienyl)-N-(4-(4-pyridinyl)methylphenyl)urea;
 N-(5-tert-butyl (1-tWa-3,4-diazolyl))-N-(4-(4-pyridyl)oxyphenyl) urea;
 N-(5-tert-butyl (1-thia-3,4-diazolyl))-N'-(3-(4-pyridyl)thiophenyl) urea;
 N-(5-tert-butyl (1-thia-3,4-diazolyl))-N'-(3-(4-methoxyphenyl)oxyphenyl) urea;
 N-(5-tert-butyl (1-thia-3,4-diazolyl))-N]-(3-(4-methylphenyl)oxyphenyl) urea;
 N-(5-tert-butyl thienyl)-N]-(4-(4-pyridyl)oxyphenyl) urea;
 N-(5-tert-butyl thienyl)-N'-(4-(4-pyridyl)thiophenyl) urea.;
 N-(5-tert-butyl thienyl)-N!-(4-(4-pyridyl)methylphenyl) urea;
 N-(5-tert-butyl tWenyl)-N'] (2,3-dichlorophenyl) urea.;
 N-(5-tert-butyl thienyl)-N'-(4-(4-hydroxyphenyl)oxyphenyl) urea;
 N-(5-tert-butyl thienyl)-N]-(4-(4-methoxyphenyl)oxyphenyl) urea;

N-(5-tert-butyl thienyl)-N-(4-(4-ethoxyphenyl)oxyphenyl) urea;
 N-(5-tert-butyl thienyl)-N]-(4-(4-isopropoxyphenyl)oxyphenyl) urea;
 and pharmaceutically acceptable salts thereof

22 A method as in claim 1 comprising administering a compound of the formula

Ra

N 0

N I-qH-C-I-qH-B

wherein R' and B are as defined in claim 1.

23 A method as in claim 22, wherein B is of the formula

X-n

-U-(Y-Q')-s-Zni

wherein Q is phenyl, Q1 is phenyl or pyridinyl, Y is --O-, -S- or CH2-, Cl, -OC2H5 or

-OC3H7, s = 0 or 1, n = 0 and n1 is 0 or 1.

24 A method as in claim 22, wherein R' is CF3- or t-butyl.

25 A method as in claim 1 comprising administering a compound of one of the formulae

R1

0 0

11

RI RI

S 0 0

II or 11

rqH-C-NH-B NH-C-NH-B

wherein R', R] and B are as defined in claim 1.

26 A method as in claim 25, wherein B is of the formula

X

n

-U--(Y- Q)-s-Zni

wherein Q is phenyl, Q1 is phenyl or pyridinyl, Y is --O- , -S- or -CH2-, Z is OH, CH3,

Cl, -OC2H5 or -OC3H7, s = 0 or 1, n = 0 and n1 is 0 or 1.

27 A method as in claim 25, wherein R1 is t-butyl.

28 A method as in claim 1, wherein the compound for formula I displays p38 activity (IC50) better than 10 μm as determined by an in-vitro kinase assay.

29 A method according to claim 1, wherein the disease is mediated by a cytokine or protease regulated by p38.

30 A method according to claim 1, comprising administering an amount of a compound of formula I effective to inhibit p38.

31 A method according to claim 1, comprising administering an amount of a compound of formula I effective to inhibit production of a disease-mediating cytokine or protease.

32 A method according to claim 1, wherein the disease is mediated by TNFα, MAT-1, MNT-3, IL-1, EL-6 or EL

. A method according to claim 1, wherein the disease is an inflammatory or immunomodulatory disease.

34 A method according to claim 1, wherein the disease is rheumatoid arthritis, osteoporosis, osteoarthritis, asthma, septic shock, inflammatory bowel disease, or the result of host-versus-graft reactions.

35 A compound of one of the formulae

a)

t-BU

N 0

1 H 11 H

0 N C-N 0 0- CH2--O

b)

t-Bu

0

1] 0

N 11

INH-C-Nw-] 0--] R6

wherein R6 is CH2-phenyl, -NH-C(O)-O-t-butyl, n-pentyl, n-butyl, -C(O)-N(CH3)2, CH2CH(CH3)2 or n-propyl;

c)

R'

N 0

N]C-N 0 CH3

H

wherein R1 is -CH2-t-butyl;

2o d)

t-Bu

N 0

1 11

N n-U-Imn

R

C1 C1

wherein R] is -CH2CF3, -C2H4 -OH, -CH2-(3-HOC6H4)] CH2C(O)NHCH3, -CH2C(O)OC2H5, -C2114CN, or

] CH2

0

1 1

O-CANH

cl cl

e)

t-Bu

N 0 0

1 H 11 H II

N C-N-] -C-O-C4H9

CH3

f)

t-Bu

0

NH-C-NHC] 0] -OCH(CH02

g)

Br

N 0

11 11 .

S- NH-C-NH-] CH3

or

h)

CH(CH3)2

CH3

N

I 0

U 11

NH-C-NH

C1 C1

and pharmaceutically acceptable salts thereof

. A pharmaceutical composition comprising a compound according to claim 35 or a pharmaceutically acceptable salt thereof and a physiologically acceptable carrier.

37 A method as in claim 1, comprising administering a compound of the formula

R'

N, :]ko

0

IN =-] I I

NH-C-NH-B

wherein R I and B are as defined in claim 1.

38 A method as in claim I comprising administering a compound of the formula

R1

0

NH-C-NH-B

wherein R' and B are as defined in claim 1.

39 A method as in claim 1, comprising administering a compound of the formula

R1

W]]k S

0

L--J, II

Imm-U-Nn-B

wherein R1, R2 and B are as defined in claim 1.

40 A method as in claim 1, comprising administering a compound of the formula

R1

I

N N*,N

k 0

N... 11

NH-C-NH-B

wherein R' and B are as defined in claim 1.

41 A method as in claim 1, comprising administering a compound of the formula

R'

0

S I I

NH-C-NH-B

wherein R1 and B are as defined in claim 1.

=>

Click on the answers from a database to select display options.

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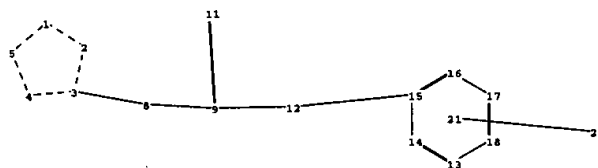
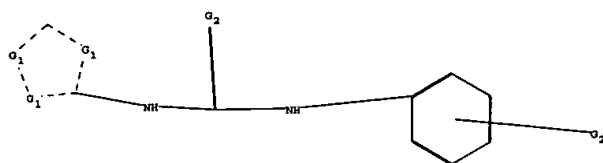
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Patent Search

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chain nodes :

8 9 11 12 20

ring nodes :

1 2 3 4 5 13 14 15 16 17 18

chain bonds :

3-8 8-9 9-11 9-12 12-15

ring bonds :

1-2 1-5 2-3 3-4 4-5 13-14 13-18 14-15 15-16 16-17 17-18

exact/norm bonds :

1-2 1-5 2-3 3-4 3-8 4-5 8-9 9-11 9-12 12-15

normalized bonds :

13-14 13-18 14-15 15-16 16-17 17-18

isolated ring systems :

containing 1 : 13 :

G1:C,O,N

G2:O,S

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 8:CLASS 9:CLASS 11:CLASS 12:CLASS 13:Atom
14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 20:CLASS 21:CLASS

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<u>NEWS 5</u>	SEP 29	DISSABS now available on STN
<u>NEWS 6</u>	OCT 10	PCTFULL: Two new display fields added
<u>NEWS 7</u>	OCT 21	BIOSIS file reloaded and enhanced
<u>NEWS 8</u>	OCT 28	BIOSIS file segment of TOXCENTER reloaded and enhanced
<u>NEWS 9</u>	NOV 24	MSDS-CCOHS file reloaded
<u>NEWS 10</u>	DEC 08	CABA reloaded with left truncation
<u>NEWS 11</u>	DEC 08	IMS file names changed
<u>NEWS 12</u>	DEC 09	Experimental property data collected by CAS now available in REGISTRY
<u>NEWS 13</u>	DEC 09	STN Entry Date available for display in REGISTRY and CA/CAPlus
<u>NEWS 14</u>	DEC 17	DGENE: Two new display fields added
<u>NEWS 15</u>	DEC 18	BIOTECHNO no longer updated
<u>NEWS 16</u>	DEC 19	CROPU no longer updated; subscriber discount no longer available
<u>NEWS 17</u>	DEC 22	Additional INPI reactions and pre-1907 documents added to CAS databases
<u>NEWS 18</u>	DEC 22	IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields
<u>NEWS 19</u>	DEC 22	ABI-INFORM now available on STN
<u>NEWS 20</u>	JAN 27	Source of Registration (SR) information in REGISTRY updated and searchable
<u>NEWS 21</u>	JAN 27	A new search aid, the Company Name Thesaurus, available in CA/CAPlus
<u>NEWS 22</u>	FEB 05	German (DE) application and patent publication number format changes
<u>NEWS 23</u>	MAR 03	MEDLINE and LMEDLINE reloaded
<u>NEWS 24</u>	MAR 03	MEDLINE file segment of TOXCENTER reloaded
<u>NEWS 25</u>	MAR 03	FRANCEPAT now available on STN
<u>NEWS 26</u>	MAR 29	Pharmaceutical Substances (PS) now available on STN
<u>NEWS 27</u>	MAR 29	WPIFV now available on STN
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<u>NEWS 29</u>	MAR 29	New monthly current-awareness alert (SDI) frequency in RAPRA
<u>NEWS EXPRESS</u>		MARCH 5 CURRENT WINDOWS VERSION IS V7.00A, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 3 MARCH 2004
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TOTAL

ENTRY

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FULL ESTIMATED COST

0.21

0.21

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L1 STRUCTURE UPLOADED

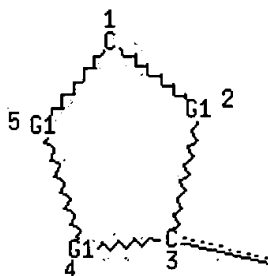
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L1 HAS NO ANSWERS

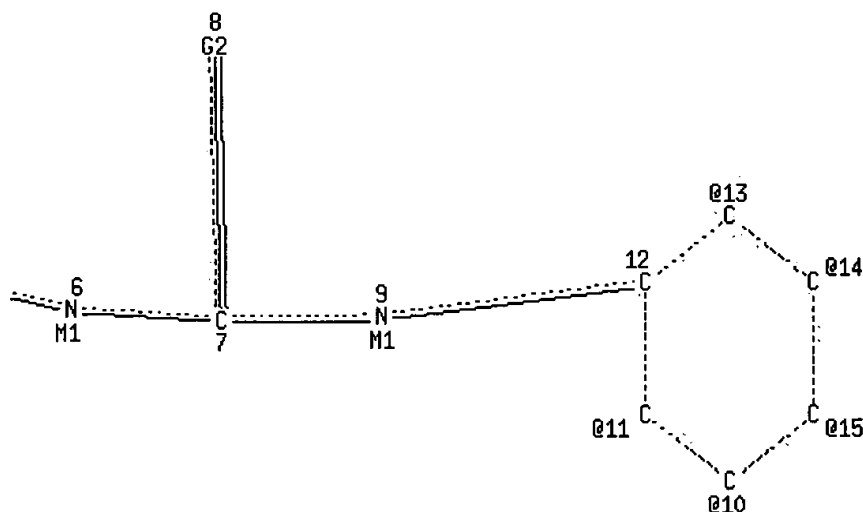
L1 STR

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G2 @16

Page 1-C

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VAR G2=20/21

VPA 16-10/11/13/14/15 S

NODE ATTRIBUTES:

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HCOUNT	IS M1	AT	9
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NSPEC	IS R	AT	2
NSPEC	IS R	AT	3
NSPEC	IS R	AT	4
NSPEC	IS R	AT	5
NSPEC	IS C	AT	6
NSPEC	IS C	AT	7
NSPEC	IS C	AT	8
NSPEC	IS C	AT	9
NSPEC	IS R	AT	10
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NSPEC	IS R	AT	14
NSPEC	IS R	AT	15
NSPEC	IS C	AT	16

DEFAULT MLEVEL IS ATOM

MLEVEL IS CLASS AT 6 7 9 20 21

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RSPEC I

NUMBER OF NODES IS 21

STEREO ATTRIBUTES: NONE

=> s 11

SAMPLE SEARCH INITIATED 21:10:28 FILE 'REGISTRY'

SAMPLE SCREEN SEARCH COMPLETED - 8160 TO ITERATE

12.3% PROCESSED 1000 ITERATIONS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)

2 ANSWERS

SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
 BATCH **COMPLETE**
 PROJECTED ITERATIONS: 157787 TO 168613
 PROJECTED ANSWERS: 84 TO 568

L2 2 SEA SSS SAM L1

=> s l1 full

THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
 DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
 FULL SEARCH INITIATED 21:10:32 FILE 'REGISTRY'
 FULL SCREEN SEARCH COMPLETED - 163349 TO ITERATE

100.0% PROCESSED 163349 ITERATIONS 787 ANSWERS
 SEARCH TIME: 00.00.03

L3 787 SEA SSS FUL L1

=> file hcaplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	155.84	156.05

FILE 'HCAPLUS' ENTERED AT 21:10:37 ON 29 MAR 2004
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FILE COVERS 1907 - 29 Mar 2004 VOL 140 ISS 14
 FILE LAST UPDATED: 28 Mar 2004 (20040328/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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(FILE 'HOME' ENTERED AT 21:09:03 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 21:09:18 ON 29 MAR 2004

L1 STRUCTURE UPLOADED

L2 2 S L1

L3 787 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 21:10:37 ON 29 MAR 2004

=> s 13/thu

151 L3
 581219 THU/RL
 L4 46 L3/THU
 (L3 (L) THU/RL)

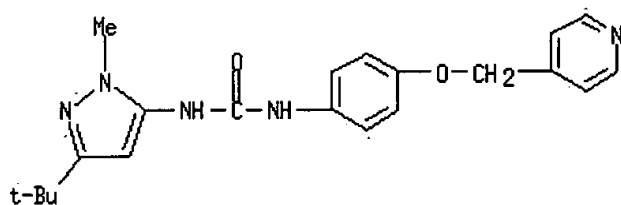
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 665 DUMAS, J?/AU
 L5 5 L4 AND DUMAS, J?/AU

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L5 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2002:407968 HCAPLUS
 DOCUMENT NUMBER: 138:49372
 TITLE: Synthesis and pharmacological characterization of a potent, orally active p38 kinase inhibitor
 AUTHOR(S): Dumas, Jacques; Hatoum-Mokdad, Holia; Sibley, Robert N.; Smith, Roger A.; Scott, William J.; Khire, Uday; Lee, Wendy; Wood, Jill; Wolanin, Donald; Cooley, Jeffrey; Bankston, Donald; Redman, Aniko M.; Schoenleber, Robert; Caringal, Yolanda; Gunn, David; Romero, Romulo; Osterhout, Martin; Paulsen, Holger; Housley, Timothy J.; Wilhelm, Scott M.; Pirro, John; Chien, Du-Shieng; Ranges, Gerald E.; Shrikhande, Alka; Muzsi, Andrew; Bortolon, Elizabeth; Wakefield, Jean; Gianpaolo Ostravage, Cynthia; Bhargava, Ajay; Chau, Thuy
 CORPORATE SOURCE: Department of Chemistry Research, Bayer Research Center, West Haven, CT, 06516, USA
 SOURCE: Bioorganic & Medicinal Chemistry Letters (2002), 12(12), 1559-1562
 CODEN: BMCLE8; ISSN: 0960-894X
 PUBLISHER: Elsevier Science Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Inhibitors of the MAP kinase p38 provide a novel approach for the treatment of osteoporosis, inflammatory disorders, and cancer. We have identified N-(3-tert-butyl-1-methyl-5-pyrazolyl)-N'-(4-(4-pyridinylmethyl)phenyl)urea as a potent and selective p38 kinase inhibitor in biochem. and cellular assays. This compd. is orally active in two acute models of cytokine release (TNF-induced IL-6 and LPS-induced TNF) and a chronic model of arthritis (20-day murine collagen-induced arthritis).
 IT 229001-93-8
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (structure-activity relationship, synthesis and pharmacol. characterization of a potent, orally active p38 kinase inhibitors)
 RN 229001-93-8 HCAPLUS
 CN Urea, N-[3-(1,1-dimethylethyl)-1-methyl-1H-pyrazol-5-yl]-N'-[4-(4-pyridinylmethoxy)phenyl]- (9CI) (CA INDEX NAME)



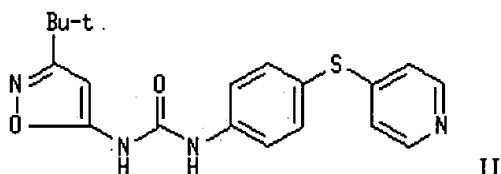
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Citing
Text References

ACCESSION NUMBER: 1999:425745 HCAPLUS
DOCUMENT NUMBER: 131:87909
TITLE: Inhibition of p38 kinase activity using substituted heterocyclic ureas
INVENTOR(S): Dumas, Jacques; Khire, Uday; Lowinger, Timothy Bruno; Paulsen, Holger; Riedl, Bernd; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia; Johnson, Jeffrey; Lee, Wendy; Redman, Aniko
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: PCT Int. Appl., 126 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932111	A1	19990701	WO 1998-US26080	19981222
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2315720	AA	19990701	CA 1998-2315720	19981222
AU 9919971	A1	19990712	AU 1999-19971	19981222
AU 739642	B2	20011018		
EP 1041982	A1	20001011	EP 1998-964709	19981222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001526223	T2	20011218	JP 2000-525102	19981222
PRIORITY APPLN. INFO.: US 1997-995750 A 19971222				
WO 1998-US26080 W 19981222				
OTHER SOURCE(S): MARPAT 131:87909				
GI				



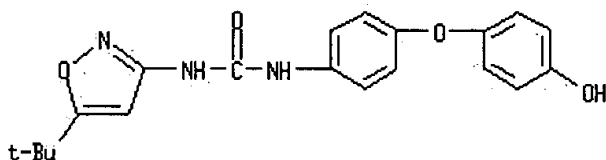
AB A method for treatment of p38-mediated disease other than cancer comprises administration of ANHCONHB [I; A = substituted isoxazoly-5-yl, pyrazoly-5-yl, thienyl, furyl; B = (substituted) mono-, di-, or tricyclic aryl, heteroaryl contg. ≥ 1 5-6 membered arom. structure contg. 0-4 N, O, or S atoms]. Reaction of 4-(4-pyridinylthio)aniline with 3-tert-butyl-5-isoxazoly-5-yl isocyanate in toluene gave title compd. II. In an in vitro p38 kinase assay, I displayed IC₅₀ values of 1-10 μ M.

IT 228999-08-4P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses) (prepn. of substituted heterocyclic ureas for treatment of p38 kinase-mediated diseases other than cancer)

RN 228999-08-4 HCAPLUS

CN Urea, N-[5-(1,1-dimethylethyl)-3-isoxazoly-5-yl]-N'-[4-(4-hydroxyphenoxy)phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT:

1

THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 1999:425744 HCAPLUS

DOCUMENT NUMBER: 131:73649

TITLE: Preparation of pyrazolyl aryl ureas and related compounds as p38 kinase inhibitors

INVENTOR(S): Dumas, Jacques; Khire, Uday; Lowinger, Timothy Bruno; Riedl, Bernd; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia; Johnson, Jeffrey; Redman, Aniko; Sibley, Robert

PATENT ASSIGNEE(S): Bayer Corporation, USA

SOURCE: PCT Int. Appl., 56 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932110	A1	19990701	WO 1998-US26079	19981222
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,				

KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,
 MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
 TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
 FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
 CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2315647 AA 19990701 CA 1998-2315647 19981222

AU 9919970 A1 19990712 AU 1999-19970 19981222

AU 762077 B2 20030619

EP 1043995 A1 20001018 EP 1998-964708 19981222

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO

JP 2001526222 T2 20011218 JP 2000-525101 19981222

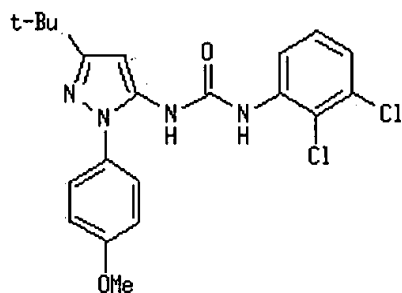
PRIORITY APPLN. INFO.:

US 1997-995751 A 19971222

WO 1998-US26079 W 19981222

OTHER SOURCE(S): MARPAT 131:73649

GI



II

AB A method for treatment of p38-mediated disease other than cancer comprises administration of ANHCONHB [I; A = substituted pyrazolyl, thienyl, furyl; B = (substituted) mono-, di-, or tricyclic aryl, heteroaryl contg.

≥1 5-6 membered arom. structure contg. 0-4 N, O, or S atoms].

Reaction of 2,3-dichlorophenyl isocyanate with 1-(4-methoxyphenyl)-3-tert-butyl-5-aminopyrazole in toluene gave title compd. II. In an in vitro p38 kinase assay, I displayed IC50 values of 1-10 μM.

IT 227623-07-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use);

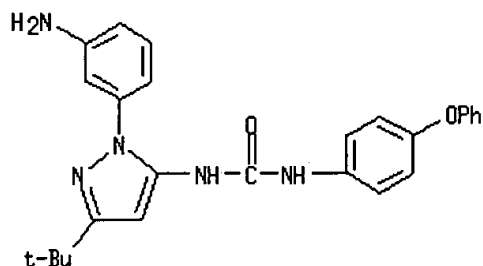
THU (Therapeutic use); BIOL (Biological study); PREP

(Preparation); RACT (Reactant or reagent); USES (Uses)

(prepn. of pyrazolyl aryl ureas and related compds. as p38 kinase inhibitors)

RN 227623-07-6 HCAPLUS

CN Urea, N-[1-(3-aminophenyl)-3-(1,1-dimethylethyl)-1H-pyrazol-5-yl]-N'-(4-phenoxyphenyl)- (9CI) (CA INDEX NAME)



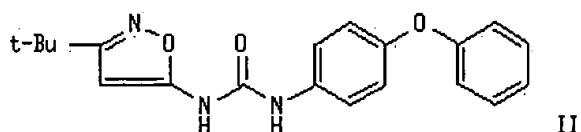
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 1999:425740 HCAPLUS
DOCUMENT NUMBER: 131:73648
TITLE: Inhibition of raf kinase using substituted heterocyclic ureas
INVENTOR(S): **Dumas, Jacques**; Khire, Uday; Lowinger, Timothy Bruno; Paulsen, Holger; Riedl, Bernd; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia; Johnson, Jeffrey; Lee, Wendy; Redman, Aniko
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: PCT Int. Appl., 163 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
<u>WO 9932106</u>	A1	19990701	<u>WO 1998-US26078</u>	19981222
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
<u>CA 2315717</u>	AA	19990701	<u>CA 1998-2315717</u>	19981222
<u>AU 9921989</u>	A1	19990712	<u>AU 1999-21989</u>	19981222
<u>EP 1047418</u>	A1	20001102	<u>EP 1998-965981</u>	19981222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
<u>JP 2001526220</u>	T2	20011218	<u>JP 2000-525097</u>	19981222
<u>BR 9814374</u>	A	20020514	<u>BR 1998-14374</u>	19981222
<u>NO 2000003232</u>	A	20000821	<u>NO 2000-3232</u>	20000621
<u>BG 104597</u>	A	20010228	<u>BG 2000-104597</u>	20000712
<u>PRIORITY APPLN. INFO.:</u>			<u>US 1997-996343</u>	A 19971222
			<u>WO 1998-US26078</u>	W 19981222
OTHER SOURCE(S):		MARPAT 131:73648		
GI				



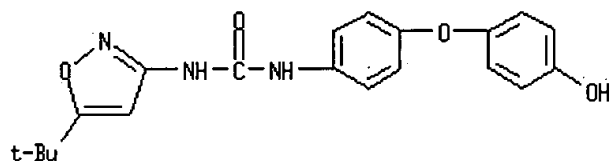
AB A method for treatment of cancerous cell growth mediated by raf kinase comprises administration of urea derivs. ANHCONHB [I; A = substituted isoxazolyl, thienyl, thiadiazolyl, furyl, pyrazolyl, etc.; B = (substituted) mono-, di-, or tricyclic aryl, heteroaryl contg. ≥ 1 5-6 membered arom. structure contg. 0-4 N, O, or S atoms]. Reaction of 4-phenyloxyphenyl isocyanate with 5-amino-3-tert-butylisoxazole in methylene chloride and heating at reflux temp. for 2 days gave title compd. II. In an in vitro raf kinase assay, I displayed IC₅₀ values of 1-10 μ M.

IT **228999-08-4P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); **THU (Therapeutic use)**; **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of substituted heterocyclic ureas for treatment of cancerous cell growth mediated by raf kinase)

RN 228999-08-4 HCAPLUS

CN Urea, N-[5-(1,1-dimethylethyl)-3-isoxazolyl]-N'-[4-(4-hydroxyphenoxy)phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT:

7

THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 1999:421660 HCAPLUS

DOCUMENT NUMBER: 131:44811

TITLE: Preparation of aryl- and heteroaryl-substituted heterocyclic ureas as raf kinase inhibitors

INVENTOR(S): **Dumas, Jacques**; Khire, Uday; Lowinger, Timothy Bruno; Paulsen, Holger; Riedl, Bernd; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia; Johnson, Jeffrey; Redman, Aniko; Sibley, Robert

PATENT ASSIGNEE(S): Bayer Corporation, USA

SOURCE: PCT Int. Appl., 58 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932455	A1	19990701	WO 1998-US26082	19981222

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,

DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2315713 AA 19990701 CA 1998-2315713 19981222

AU 9919055 A1 19990712 AU 1999-19055 19981222

AU 765412 B2 20030918

EP 1056725 A1 20001206 EP 1998-963810 19981222

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

BR 9814361 A 20011127 BR 1998-14361 19981222

JP 2001526269 T2 20011218 JP 2000-525392 19981222

CN 1117081 B 20030806 CN 1998-812504 19981222

NZ 505845 A 20031031 NZ 1998-505845 19981222

NO 2000003231 A 20000822 NO 2000-3231 20000621

BG 104598 A 20010228 BG 2000-104598 20000712

PRIORITY APPLN. INFO.:

US 1997-996181 A 19971222

WO 1998-US26082 W 19981222

OTHER SOURCE(S): MARPAT 131:44811

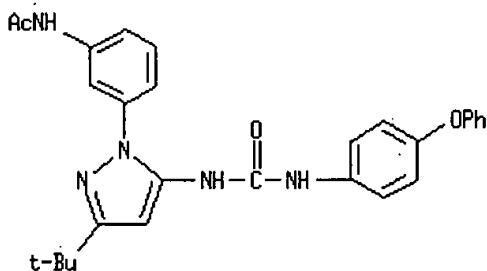
AB The title compds. ANHCONHB (A = heteroaryl; B = aryl, heteroaryl), raf kinase inhibitors, were prepd. E.g., N-(1-phenyl-3-tert-butyl-5-pyrazolyl)-N'-(4-(4-pyridinylmethyl)phenyl)urea was prepd.

IT 227623-06-5P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of aryl- and heteroaryl-substituted heterocyclic ureas as raf kinase inhibitors)

RN 227623-06-5 HCAPLUS

CN Acetamide, N-[3-[3-(1,1-dimethylethyl)-5-[[[(4-phenoxyphenyl)amino]carbonyl]amino]-1H-pyrazol-1-yl]phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 21:09:03 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 21:09:18 ON 29 MAR 2004

L1 STRUCTURE UPLOADED

L2 2 S L1

L3 787 S L1 FULL

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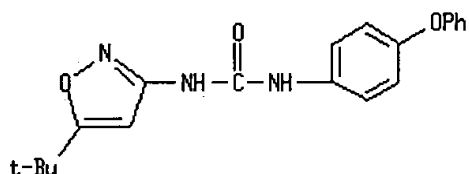
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 L8 1 L6 AND LOWINGER, T?/AU

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L8 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
ACCESSION NUMBER:	2001:746592 HCAPLUS
DOCUMENT NUMBER:	136:95577
TITLE:	Discovery of heterocyclic ureas as a new class of raf kinase inhibitors: identification of a second generation lead by a combinatorial chemistry approach
AUTHOR(S):	Smith, R. A.; Barbosa, J.; Blum, C. L.; Bobko, M. A.; Caringal, Y. V.; Dally, R.; Johnson, J. S.; Katz, M. E.; Kennure, N.; Kingery-Wood, J.; Lee, W.; Lowinger, T. B.; Lyons, J.; Marsh, V.; Rogers, D. H.; Swartz, S.; Walling, T.; Wild, H.
CORPORATE SOURCE:	Department of Chemistry Research, Bayer Research Center, West Haven, CT, 06516, USA
SOURCE:	Bioorganic & Medicinal Chemistry Letters (2001), 11(20), 2775-2778 CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER:	Elsevier Science Ltd.
DOCUMENT TYPE:	Journal
LANGUAGE:	English
AB	Heterocyclic ureas, such as N-3-thienyl N'-aryl ureas, have been identified as novel inhibitors of raf kinase, a key mediator in the ras signal transduction pathway. Structure-activity relationships were established, and the potency of the screening hit was improved 10-fold to IC50=1.7 µM. A combinatorial synthesis approach enabled the identification of a breakthrough lead (IC50=0.54 µM) for a second generation series of heterocyclic urea raf kinase inhibitors.
IT	228998-90-1P RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (heterocyclic ureas as raf kinase inhibitors)
RN	228998-90-1 HCAPLUS
CN	Urea, N-[5-(1,1-dimethylethyl)-3-isoxazolyl]-N'-(4-phenoxyphenyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 21:09:03 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 21:09:18 ON 29 MAR 2004

L1 STRUCTURE UPLOADED

L2 2 S L1

L3 787 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 21:10:37 ON 29 MAR 2004

L4 46 S L3/THU

L5 5 S L4 AND DUMAS, J?/AU

L6 41 S L4 NOT L5

L7 0 S L6 AND KHIRE, U?/AU

L8 1 S L6 AND LOWINGER, T?/AU

=> s l6 and paulsen, h?/au

660 PAULSEN, H?/AU

L9 1 L6 AND PAULSEN, H?/AU

=> s l6 not l8

L10 40 L6 NOT L8

=> s l10 and paulsen, h?/au

660 PAULSEN, H?/AU

L11 1 L10 AND PAULSEN, H?/AU

=> d l11, ibib abs fhitr, 1

L11 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 1998:776671 HCAPLUS

DOCUMENT NUMBER: 130:38286

TITLE: Inhibition of p38 kinase activity by aryl ureas

INVENTOR(S): Ranges, Gerald; Scott, William; Bombara, Michael; Rauner, Deborah; Redman, Aniko; Smith, Roger; Paulsen, Holger; Chen, Jinshan; Gunn, David; Renick, Joel

PATENT ASSIGNEE(S): Bayer Corp., USA; et al.

SOURCE: PCT Int. Appl., 84 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9852558	A1	19981126	WO 1998-US10375	19980521

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9875854 A1 19981211 AU 1998-75854 19980521

EP 1019040 A1 20000719 EP 1998-923600 19980521

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

JP 2001526687 T2 20011218 JP 1998-550617 19980521

US 6344476 B1 20020205 US 1998-83396 19980522

US 2002103253 A1 20020801 US 2001-947761 20010907

PRIORITY APPLN. INFO.:

US 1997-863022 A2 19970523

US 1997-98557P P 19970523

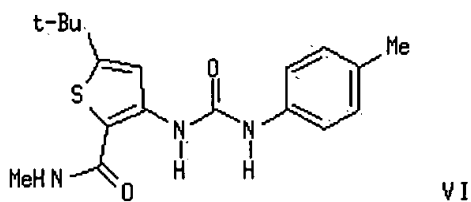
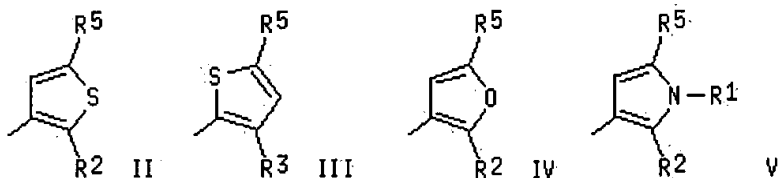
WO 1998-US10375 W 19980521

US 1998-83396 A3 19980522

OTHER SOURCE(S):

MARPAT 130:38286

GI



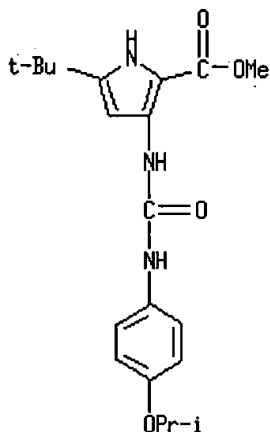
AB The title ureas ANHC(O)NHB [I; A = (un)substituted C6-12 aryl, C5-12 heteroaryl; B = II-V; R1 = H, C1-4 alkyl; R2, R3 = halo, COOR1, CN, etc.; R5 = C3-5 alkyl], useful in treating cytokine mediated diseases other than cancer and proteolytic enzyme mediated diseases other than cancer, were prepd. Thus, reaction of N-methyl-3-amino-5-tert-butylthiophene-2-carboxamide (prepn. given) with 4-methylphenyl isocyanate in PhMe afforded 44% the title compd. VI. Compds. I are useful in treating diseases mediated by TNF α , MMP-1, MMP-3, IL-1, IL-6, or IL-8 such as rheumatoid arthritis, osteoporosis, asthma, septic shock, inflammatory bowel disease, or the result of host-vs.-graft reactions. All exemplified compds. I showed p38 IC50s of 1 nM - 10 μ M.

IT 216573-97-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (inhibition of p38 kinase activity by aryl ureas)

RN 216573-97-6 HCAPLUS

CN 1H-Pyrrole-2-carboxylic acid, 5-(1,1-dimethylethyl)-3-[[[4-(1-methylethoxy)phenyl]amino]carbonyl]amino]-, methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 21:09:03 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 21:09:18 ON 29 MAR 2004

L1 STRUCTURE UPLOADED
L2 2 S L1
L3 787 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 21:10:37 ON 29 MAR 2004

L4 46 S L3/THU
L5 5 S L4 AND DUMAS, J?/AU
L6 41 S L4 NOT L5
L7 0 S L6 AND KHIRE, U?/AU
L8 1 S L6 AND LOWINGER, T?/AU
L9 1 S L6 AND PAULSEN, H?/AU
L10 40 S L6 NOT L8
L11 1 S L10 AND PAULSEN, H?/AU

=> s l10 not l11

L12 39 L10 NOT L11

=> s l12 and riedl, b?/au

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L13 0 L12 AND RIEDL, B?/AU

=> s l12 and scott, w?/au

1938 SCOTT, W?/AU
L14 0 L12 AND SCOTT, W?/AU

=> s l12 and smith, r?/au

13382 SMITH, R?/AU
L15 0 L12 AND SMITH, R?/AU

=> s l12 and wood, w?/au

1755 WOOD, W?/AU

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=> s 112 and hatoum-mokdad, h?/au
      26 HATOUM-MOKDAD, H?/AU
L17          0 L12 AND HATOUM-MOKDAD, H?/AU

=> s 112 and johnson, j?/au
      7563 JOHNSON, J?/AU
L18          0 L12 AND JOHNSON, J?/AU

=> s 112 and lee, w?/au
      8561 LEE, W?/AU
L19          0 L12 AND LEE, W?/AU

=> s 112 and redman, a?/au
      30 REDMAN, A?/AU
L20          0 L12 AND REDMAN, A?/AU

=> s 112 and sibley, r?/au
      189 SIBLEY, R?/AU
L21          0 L12 AND SIBLEY, R?/AU

=> s 112 and renick, j?/au
      14 RENICK, J?/AU
L22          0 L12 AND RENICK, J?/AU

=> d his

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(FILE 'HOME' ENTERED AT 21:09:03 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 21:09:18 ON 29 MAR 2004

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L1          STRUCTURE UPLOADED
L2          2 S L1
L3          787 S L1 FULL

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FILE 'HCAPLUS' ENTERED AT 21:10:37 ON 29 MAR 2004

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L4          46 S L3/THU
L5          5 S L4 AND DUMAS, J?/AU
L6          41 S L4 NOT L5
L7          0 S L6 AND KHIRE, U?/AU
L8          1 S L6 AND LOWINGER, T?/AU
L9          1 S L6 AND PAULSEN, H?/AU
L10         40 S L6 NOT L8
L11         1 S L10 AND PAULSEN, H?/AU
L12         39 S L10 NOT L11
L13         0 S L12 AND RIEDL, B?/AU
L14         0 S L12 AND SCOTT, W?/AU
L15         0 S L12 AND SMITH, R?/AU
L16         0 S L12 AND WOOD, W?/AU
L17         0 S L12 AND HATOUM-MOKDAD, H?/AU
L18         0 S L12 AND JOHNSON, J?/AU
L19         0 S L12 AND LEE, W?/AU
L20         0 S L12 AND REDMAN, A?/AU
L21         0 S L12 AND SIBLEY, R?/AU
L22         0 S L12 AND RENICK, J?/AU

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      240211 CANC?
L23          5 L12 AND  CANC?

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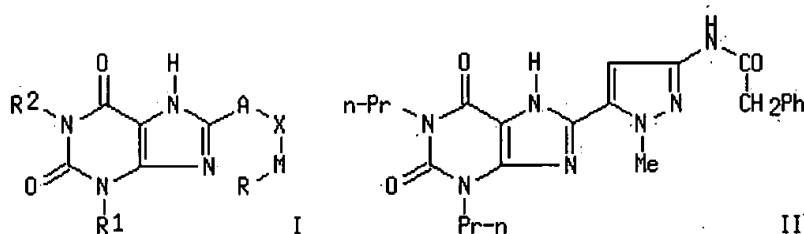
=> d 123, ibib abs fhitr, 1-5

L23 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2003:610209 HCAPLUS
DOCUMENT NUMBER: 139:164659
TITLE: Preparation of 8-heteroaryl xanthine adenosine A2B
receptor antagonists for use in pharmaceutical
compositions
INVENTOR(S): Baraldi, Pier Giovanni; Borea, Pier A.
PATENT ASSIGNEE(S): King Pharmaceuticals Research and Development, Inc.,
USA
SOURCE: PCT Int. Appl., 135 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003063800	A2	20030807	WO 2003-US3224	20030203
WO 2003063800	A3	20031224		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG US 2003207879 A1 20031106 US 2003-357865 20030203 PRIORITY APPLN. INFO.: US 2002-353317P P 20020201 OTHER SOURCE(S): MARPAT 139:164659 GI				



AB 8-Heteroaryl xanthines, such as I [R = aryl, heteroaryl, amino, carboxy, NO₂, OH, etc; R₁, R₂ = H, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl; R₃ = H, alkyl, alkenyl, alkynyl; A = bond, alkylene, alkenylene, alkynylene; M = bond, carbonyl contg. alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, heteroalkynylene, etc.; X = 5 or 6 membered heterocyclic ring], were prepd. for therapeutic use as adenosine A2B receptor antagonists. These 8-heteroaryl xanthines are useful for treatment of autoimmune, inflammatory, and vascular diseases which are mediated by adenosine A2B receptors such as, retinal vascular diseases, acute inflammatory diseases involving degranulation of mast

cells including asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, allergic rhinitis, allergic dermatitis and bee sting, impaired sensitivity to insulin including type 2 diabetes or non-insulin dependent diabetes, pre-diabetic state, impaired glucose tolerance, diseases in which angiogenesis is a key component of pathogenesis, including solid tumors and angiogenic retinopathy, apnea of pre-term infants, myocardial reperfusion injury, inflammatory bowel disease, multiple sclerosis, and lupus erythematosus. Thus, II was prepd. via a cyclocondensation reaction of 1-methyl-3-(benzyloxycarbonylamino)pyrazole-5-carboxylic acid with 1,3-dipropyl-5,6-diaminouracil using EDCI in MeOH to form the pyrazolylxanthine moiety and subsequent N-acylation with phenylacetic acid using thionyl chloride and Et₃N in CH₂Cl₂. The prepd. xanthines were tested for affinity to human A₁, A_{2A}, A_{2B}, and A₃ adenosine receptors.

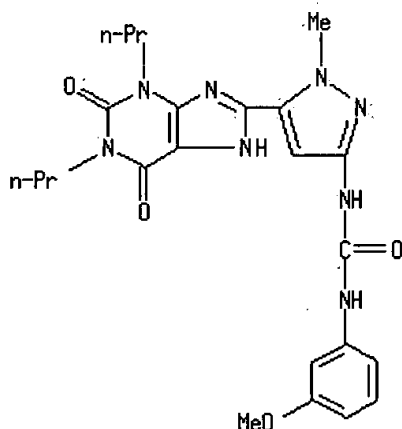
IT **574754-45-3P**

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of 8-heteroaryl-xanthine adenosine A_{2B} receptor antagonists for use in pharmaceutical compns. for treatment of inflammatory, autoimmune and retinal vascular diseases)

RN **574754-45-3** HCAPLUS

CN Urea, N-(3-methoxyphenyl)-N'-[1-methyl-5-(2,3,6,7-tetrahydro-2,6-dioxo-1,3-dipropyl-1H-purin-8-yl)-1H-pyrazol-3-yl]- (9CI) (CA INDEX NAME)



L23 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2002:849617 HCAPLUS

DOCUMENT NUMBER: 137:370101

TITLE: Preparation of quinoline derivatives having azolyl group and quinazoline derivatives as antitumor agents
 INVENTOR(S): Kubo, Kazuo; Sakai, Teruyuki; Nagao, Rika; Fujiwara, Yasunari; Isoe, Toshiyuki; Hasegawa, Kazumasa

PATENT ASSIGNEE(S): Kirin Beer Kabushiki Kaisha, Japan

SOURCE: PCT Int. Appl., 89 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

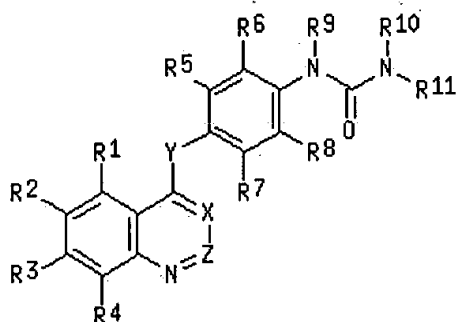
LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2002088110	A1	20021107	WO 2002-JP4279	20020426
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
JP 2003012668	A2	20030115	JP 2002-126869	20020426
US 2003087907	A1	20030508	US 2002-132473	20020426
EP 1382604	A1	20040121	EP 2002-724651	20020426
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
NO 2003004595	A	20031219	NO 2003-4595	20031014
PRIORITY APPLN. INFO.:			JP 2001-132775	A 20010427
			WO 2002-JP4279	W 20020426
OTHER SOURCE(S):		MARPAT 137:370101		
GI				



AB N-[(4-quinolinyl or 4-quinazolinyl)thio or -oxy]phenyl-N'-azolyurea derivs. represented by the formula (I) or pharmaceutically acceptable salts or solvates thereof [wherein X, Z = CH, N; Y = O, S; R1, R2, R3 = H, NO2, NH2, each (un)substituted C1-6 alkyl or alkoxy or C2-6 alkenyl or alkynyl; R4 = H; R5-R8 = H, halo, C1-4 alkyl, alkoxy, or alkylthio, CF3, NO2, NH2; R9, R10 = C1-6 alkyl, each (un)substituted C1-4 alkylcarbonyl or C1-6 alkyl; R11 = (un)substituted azolyl] are prepd. These compds. are useful for the treatment of tumor, diabetic retinopathy, chronic articular rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma. They are also used for inhibiting neovascularization of a target blood vessel by contacting them with vascular endothelial cells of the target blood vessel. Thus, 100 mg 2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]aniline was dissolved in 5 mL CHCl₃ and 0.5 mL Et₃N, treated with a soln. of 100 mg triphosgene in CHCl₃, and stirred at room temp. for 15 min, followed by adding 49 mg 2-aminothiazole, and the resulting mixt. was stirred at room temp. overnight to give 31 mg N-[2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl]-N'-(1,3-thiazol-2-yl)urea (II). II at 20 mg/kg/day for 9 days inhibited the growth of human lung cancer transplanted in nude mice by 92.0%. The compds. I in vitro showed IC₅₀ of 0.001-0.0697 μ M for inhibiting the phosphorylation of the intracellular domain of human vascular endothelial cell growth factor (VEGF) receptor KDR (kinase insert domain-contg. receptor) in IH3T3 cell expressing human KDR.

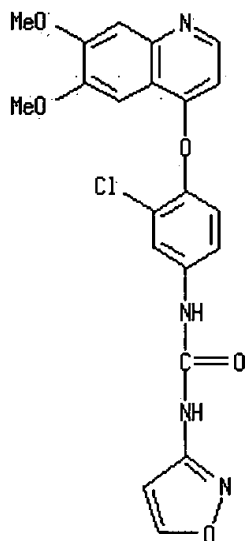
IT 475108-15-7P, N-[3-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-N'-(3-isoxazolyl)urea

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU** (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of N-[(4-quinolinyl or 4-quinazolinyl)oxy]phenyl-N'-azolyurea derivs. as neovascularization inhibitors for treatment of tumor, diabetic retinopathy, chronic articular rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma)

RN 475108-15-7 HCAPLUS

CN Urea, N-[3-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-3-isoxazolyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT:

24

THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2002:314913 HCAPLUS

DOCUMENT NUMBER: 136:340689

TITLE: Preparation of urea derivatives containing nitrogenous aromatic ring compounds as inhibitors of angiogenesis
 FUNAHASHI, Yasuhiro; TSURUOKA, Akihiko; MATSUKURA, Masayuki; HANEDA, Toru; FUKUDA, Yoshio; KAMATA, Junichi; TAKAHASHI, Keiko; MATSUSHIMA, Tomohiro; MIYAZAKI, Kazuki; NOMOTO, Kenichi; WATANABE, Tatsuo; OBAISHI, Hiroshi; YAMAGUCHI, Atsumi; SUZUKI, Sachi; NAKAMURA, KATSUJI; MIMURA, Fusayo; YAMAMOTO, YUJI; MATSUI, JUNJI; MATSUI, Kenji; YOSHIBA, Takako; SUZUKI, Yasuyuki; ARIMOTO, Itaru

INVENTOR(S):

PATENT ASSIGNEE(S): Eisai Co., Ltd., Japan

SOURCE: PCT Int. Appl., 699 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002032872	A1	20020425	WO 2001-JP9221	20011019

WO 2002032872 C1 20020926

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001095986 A5 20020429 AU 2001-95986 20011019

NO 2003001731 A 20030619 NO 2003-1731 20030414

US 2004053908 A1 20040318 US 2003-420466 20030418

PRIORITY APPLN. INFO.:

JP 2000-320420 A 20001020

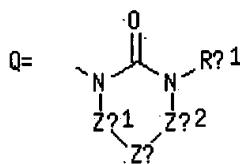
JP 2000-386195 A 20001220

JP 2001-46685 A 20010222

WO 2001-JP9221 W 20011019

OTHER SOURCE(S): MARPAT 136:340689

GI



AB N-aryl or N-heteroarylurea derivs. represented by the general formula Ag-Xg-Yg-Tg1 or salts thereof, or hydrates of both [wherein Ag = (un)substituted C6-14 aryl or 5- to 14-membered heterocyclic group; Xg = single bond, O, S, C1-6 alkylene, SO, SO2, (un)substituted NH; Yg = (un)substituted C6-14 aryl, 5- to 14-membered heterocyclic group, C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl-C1-6 alkyl, 5- to 14-membered heteroaryl-C1-6 alkyl, (CH2)gSO2 (g = 1-8), (CH2)faCH:CH(CH2)fb (fa, fb = 0, 1, 2, 3), etc.; and Tg1 = a group of the general formula -Eg-CO-NRg1(Zg) or Q; wherein Eg = a single bond, (un)substituted NH; Rg1 = H, (un)substituted C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-8 aliph. hydrocarbyl, etc.; Zg = C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl, etc.; Zg1, Zg2 = (a) a single bond, (b) C1-6 alkylene optionally having ≥ 1 atoms selected from O, S, and N in the middle or the terminus of the chain and optionally substituted with oxo, (c) (un)substituted C2-6 alkenyl] are prepd. These compds. are also inhibitors of vascular endothelial growth factor receptor kinase (VEGFR2 kinase) and are useful as antitumor agents against hemangioma, pancreatic cancer, stomach cancer, colon cancer, breast cancer, prostate cancer, lung cancer, brain tumor, leukemia, or ovarian cancer, as cancer metastasis inhibitors, and for the treatment of retina neovascularization, diabetic retinopathy, atherosclerosis, or inflammatory diseases such as osteoarthritis, rheumatoid arthritis, psoriasis, or delayed hypersensitivity. Thus, to soln. of 334 mg 4-[6-(4-benzyloxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenylamine in 4 mL DMF were added 0.066 mL pyridine and 0.102 mL Ph chlorocarbonate and stirred at room temp. for 2.5 h to give 330 mg N-[4-[6-(4-benzyloxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea which (260 mg) was hydrogenolyzed over platinum oxide in ethanol overnight to give 160 mg N-[4-[6-(4-hydroxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea (I). I showed IC50 of 0.02 nM

for inhibiting the vascular endothelial growth factor (VEGF)-stimulated sandwich tube formation in vascular endothelial cell.

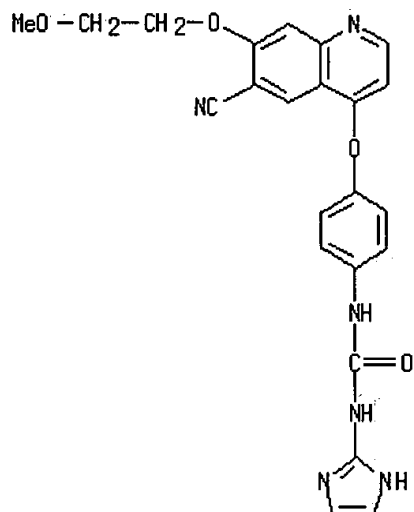
IT **417713-01-0P**

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU** (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of urea derivs. contg. nitrogenous arom. ring compds. as angiogenesis inhibitors for prevention or treatment of diseases)

RN **417713-01-0** HCAPLUS

CN Urea, N-[4-[[6-cyano-7-(2-methoxyethoxy)-4-quinolinyl]oxy]phenyl]-N'-1H-imidazol-2-yl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 17

THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:137022 HCAPLUS

DOCUMENT NUMBER: 134:193431

TITLE: 3(5)-Ureidopyrazole derivatives, processes for their preparation and their therapeutic uses including antitumor agents

INVENTOR(S): Pevarello, Paolo; Orsini, Paolo; Traquandi, Gabriella; Varasi, Mario; Fritzen, Edward L.; Warpehoski, Martha A.; Pierce, Betsy S.

PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy; Pharmacia & Upjohn Company

SOURCE: PCT Int. Appl., 54 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012188	A1	20010222	WO 2000-US17878	20000811
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,				

LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6387900 B1 20020514 US 1999-372833 19990812

EP 1202734 A1 20020508 EP 2000-955241 20000811

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL

BR 2000013277 A 20020618 BR 2000-13277 20000811

JP 2003507328 T2 20030225 JP 2001-516534 20000811

ZA 2002001118 A 20030310 ZA 2002-1118 20020208

NO 2002000687 A 20020403 NO 2002-687 20020211

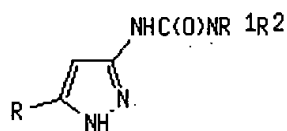
PRIORITY APPLN. INFO.:

US 1999-372833 A 19990812

WO 2000-US17878 W 20000811

OTHER SOURCE(S): MARPAT 134:193431

GI



I

AB Compds. which are 3(5)-ureidopyrazole derivs. (I; e.g. N-(5-cyclopropyl-1H-pyrazol-3-yl)-N'-[2-(1-piperidinyl)ethyl]urea) or a pharmaceutically acceptable salt thereof, processes for their prepn. and their use as antitumor agents are claimed. In I: R = C1-C6 alkyl, aryl or arylalkyl group, which is optionally substituted with ≥ 1 OH, halogen, nitro, cyano, oxo, carboxy, amino, alkylamino, dialkylamino, alkylcarbonylamino, alkoxycarbonylamino, alkoxycarbonylalkylamino, aminocarbonylalkylamino, N-alkyl-N-carbonylamino, N-cycloalkyl-N-alkylaminoalkyl, aminoalkyl, aminocarbonyl, alkyl, cycloalkyl, alkylthio, alkoxy, alkylcarbonyl, alkylsulfonyl, alkylsulfonylamino, aminosulfonyl, alkoxycarbonyl, aryl, arylalkyl, aryloxy, arylthio, arylsulfonyl, arylamino, arylcarbonyl, N-alkylpiperazinyl, 4-morpholinyl, perfluorinated C1-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C2-C4 aminoalkynyl or C2-C4 hydroxyalkynyl substituents. R₁ = -(CH₂)_n-R₃. N = 0-4. R₃ = H, OH, amino, cycloalkyl, aryl and heterocyclyl, which is optionally substituted with ≥ 1 OH, halogen, nitro, cyano, oxo, carboxy, amino, alkylamino, dialkylamino, alkylcarbonylamino, alkoxycarbonylamino, alkoxycarbonylalkylamino, aminocarbonylalkylamino, N-alkyl-N-carbonylamino, N-cycloalkyl-N-alkylaminoalkyl, aminoalkyl, aminocarbonyl, alkyl, cycloalkyl, alkylthio, alkoxy, alkylcarbonyl, alkylsulfonyl, alkylsulfonylamino, aminosulfonyl, alkoxycarbonyl, aryl, arylalkyl, aryloxy, arylthio, arylsulfonyl, arylamino, arylcarbonyl, N-alkylpiperazinyl, 4-morpholinyl, perfluorinated C1-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C2-C4 aminoalkynyl or C2-C4 hydroxyalkynyl substituents. R₂ = H, or R₂ and R₁, together with the N atom to which they are bonded, form a heterocyclyl or heteroaryl group, which is optionally substituted with ≥ 1 OH, halogen, nitro, cyano, oxo, carboxy, amino, alkylamino, dialkylamino, alkylcarbonylamino, alkoxycarbonylamino, alkoxycarbonylalkylamino, aminocarbonylalkylamino, N-alkyl-N-carbonylamino, N-cycloalkyl-N-alkylaminoalkyl, aminoalkyl, aminocarbonyl, alkyl, cycloalkyl, alkylthio, alkoxy, alkylcarbonyl, alkylsulfonyl, alkylsulfonylamino, aminosulfonyl, alkoxycarbonyl, aryl, arylalkyl, aryloxy, arylthio, arylsulfonyl, arylamino, arylcarbonyl, N-alkylpiperazinyl, 4-morpholinyl, perfluorinated C1-C4 alkyl, C2-C4

alkenyl, C2-C4 alkynyl, C2-C4 aminoalkynyl or C2-C4 hydroxyalkynyl substituents. When n is 0 and R₂ is H, R is a C3-C6 cycloalkyl group optionally substituted with a straight or branched C1-C6 alkyl group. The compds. are useful for the treatment of **cancer**, cell proliferative disorders, Alzheimer's disease, viral infections, auto-immune diseases or neurodegenerative diseases, but no quant. test results are presented. The **cancer** is selected from carcinoma, squamous cell carcinoma, hematopoietic tumors of myeloid or lymphoid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoacanthoma, thyroid follicular **cancer** and Kaposi's sarcoma. The cell proliferative disorder is selected from benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation assocd. with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis. The method of treatment provides tumor angiogenesis and metastasis inhibition, cell cycle inhibition or cdk/cyclin dependent inhibition, and treatment or prevention of radiotherapy-induced or chemotherapy-induced alopecia. A process for prepg. I comprises : (a) reacting a 3-amino-5-R-1H-pyrazole with a R₁NCO to produce a 1-R₁NHC(O)-3-R₁NHC(O)NH-5-R-1H-pyrazole and (b) selectively hydrolyzing this intermediate in a basic medium to produce I. Another method comprises (c) reacting a 1-tert-butoxycarbonyl-3-amino-5-R-1H-pyrazole with 4-nitrophenyl chloroformate, or a polymer supported form of 4-nitrophenyl chloroformate, to produce a 1-tert-butoxycarbonyl-3-(4-nitrophenoxycarbonylamino)-5-R-1H-pyrazole, or a polymer supported form; (d) reacting this intermediate with a R₁R₂NH to produce a 1-tert-butoxycarbonyl-3-(R₁R₂NC(O)NH)-5-R-1H-pyrazole; (e) hydrolyzing this compd. in acidic medium to produce I; and, optionally, converting the 3-ureidopyrazole deriv. into another deriv., and/or into a salt thereof.

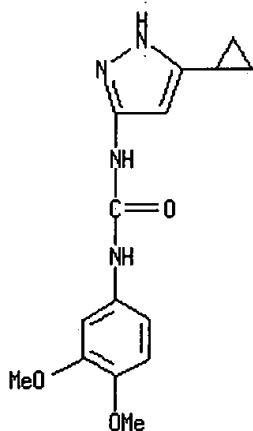
IT **326920-53-0P**, N-(5-Cyclopropyl-1H-pyrazol-3-yl)-N'-(3,4-dimethoxyphenyl)urea

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

(ureidopyrazole derivs., processes for prepn. and therapeutic uses including antitumor agents)

RN **326920-53-0** HCAPLUS

CN Urea, N-(5-cyclopropyl-1H-pyrazol-3-yl)-N'-(3,4-dimethoxyphenyl)- (9CI)
(CA INDEX NAME)



REFERENCE COUNT:

1

THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

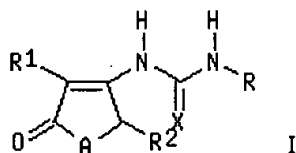
L23 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 1999:194134 HCAPLUS
 DOCUMENT NUMBER: 130:237458
 TITLE: Preparation of ureido and thioureido derivatives of
 4-amino-2(5H)-furanones and 4-amino-2(5H)-thiophenones
 as antitumor agents
 INVENTOR(S): Menta, Ernesto; Pescalli, Nicoletta; Conti, Marco;
 Zimmermann, Gerd
 PATENT ASSIGNEE(S): Roche Diagnostics G.m.b.H., Germany
 SOURCE: PCT Int. Appl., 28 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
<u>WO 9912917</u>	A1	19990318	<u>WO 1998-EP5524</u>	19980901
W:		AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM		
RW:		GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG		
<u>CA 2302284</u>	AA	19990318	<u>CA 1998-2302284</u>	19980901
<u>AU 9895350</u>	A1	19990329	<u>AU 1998-95350</u>	19980901
<u>AU 748490</u>	B2	20020606		
<u>EP 1009747</u>	A1	20000621	<u>EP 1998-948889</u>	19980901
R:		AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI		
<u>BR 9812629</u>	A	20000822	<u>BR 1998-12629</u>	19980901
<u>JP 2001515894</u>	T2	20010925	<u>JP 2000-510725</u>	19980901
<u>ZA 9808096</u>	A	20000322	<u>ZA 1998-8096</u>	19980904
<u>US 6333346</u>	B1	20011225	<u>US 2000-485709</u>	20000602
<u>US 2002058694</u>	A1	20020516	<u>US 2001-986310</u>	20011108
PRIORITY APPLN. INFO.:			<u>EP 1997-115391</u>	A 19970905
			<u>WO 1998-EP5524</u>	W 19980901
			<u>US 2000-485709</u>	A3 20000602

OTHER SOURCE(S): MARPAT 130:237458
 GI



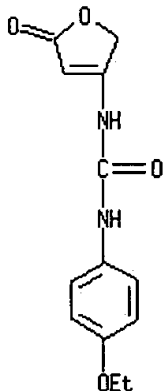
AB The title compds. [I; A = O, S; X = O, S; R1, R2 = H, alkyl; R = alkyl, cycloalkyl, alkylthio, etc.], useful as antitumor agents, esp. against colon **cancers**, were prepd. Thus, reaction of 4-chlorophenylurea with Et 4-chloroacetoacetate afforded I [A = O; X = O; R1 = R2 = H; R = 4-ClC6H4] which showed IC50 of 0.032 Tg/mL and of 0.034 Tg/mL against human colon **cancer** cell lines HT 29 and HCT 116, resp.

IT 221290-98-8P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of ureido and thioureido derivs. of 4-amino-2(5H)-furanones and 4-amino-2(5H)-thiophenones as antitumor agents)

RN 221290-98-8 HCAPLUS

CN Urea, N-(2,5-dihydro-5-oxo-3-furanyl)-N'-(4-ethoxyphenyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 21:09:03 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 21:09:18 ON 29 MAR 2004

L1 STRUCTURE UPLOADED

L2 2 S L1

L3 787 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 21:10:37 ON 29 MAR 2004

L4 46 S L3/THU

L5 5 S L4 AND DUMAS, J?/AU

L6 41 S L4 NOT L5

L7 0 S L6 AND KHIRE, U?/AU

L8 1 S L6 AND LOWINGER, T?/AU

L9 1 S L6 AND PAULSEN, H?/AU

L10 40 S L6 NOT L8

L11 1 S L10 AND PAULSEN, H?/AU

L12 39 S L10 NOT L11

L13 0 S L12 AND RIEDL, B?/AU

L14 0 S L12 AND SCOTT, W?/AU

L15 0 S L12 AND SMITH, R?/AU

L16 0 S L12 AND WOOD, W?/AU

L17 0 S L12 AND HATOUM-MOKDAD, H?/AU

L18 0 S L12 AND JOHNSON, J?/AU

L19 0 S L12 AND LEE, W?/AU

L20 0 S L12 AND REDMAN, A?/AU

L21 0 S L12 AND SIBLEY, R?/AU

L22 0 S L12 AND RENICK, J?/AU

L23 5 S L12 AND CANC?

=> s l12 not l23

L24 34 L12 NOT L23

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277 'L24'

14 IBIB

212191 ABS

5 ABSES

212196 ABS

(ABS OR ABSES)

0 FHITSTR

7847829 1

261226 34

L25 0 L24, IBIB ABS FHITSTR, 1-34

('L24' (W) IBIB (W) ABS (W) FHITSTR (W) 1 (W) 34)

=> d 124, ibib abs fhitr, 1-34

L24 ANSWER 1 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full
Text

Citing
References

ACCESSION NUMBER:

2004:182368 HCAPLUS

TITLE:

Three hybrid assay system for isolating ligand-binding polypeptides and for isolating small mol. ligands

INVENTOR(S):

Come, Jon H.; Becker, Frank; Kley, Nikolai A.; Reichel, Christoph

PATENT ASSIGNEE(S):

USA

SOURCE:

U.S. Pat. Appl. Publ., 238 pp., Cont.-in-part of U.S. Ser. No. 91,177.

CODEN: USXXCO

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004043388	A1	20040304	US 2002-234985	20020903
US 2003165873	A1	20030904	US 2002-91177	20020304

PRIORITY APPLN. INFO.:

US 2001-272932P	P	20010302
US 2001-278233P	P	20010323
US 2001-329437P	P	20011015
US 2002-91177	A2	20020304

AB The invention provides compns. and methods for isolating ligand-binding polypeptides for a user-specified ligand, and for isolating small mol. ligands for a user-specified target polypeptide using an improved class of hybrid ligand compds. Prepn. of compds., e.g a methotrexate moiety linked by a polyethylene glycol moiety to dexamethasone, is described.

IT INDEXING IN PROGRESS

IT **228999-48-2D**, conjugates

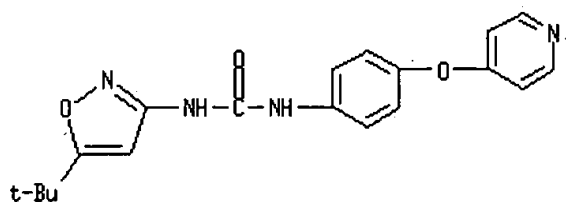
RL: BUU (Biological use, unclassified); **THU (Therapeutic use)**;

BIOL (Biological study); USES (Uses)

(three hybrid assay system for isolating ligand-binding polypeptides and for isolating small mol. ligands)

RN **228999-48-2** HCAPLUS

CN Urea, N-[5-(1,1-dimethylethyl)-3-isoxazolyl]-N'-[4-(4-pyridinyloxy)phenyl]-
(9CI) (CA INDEX NAME)

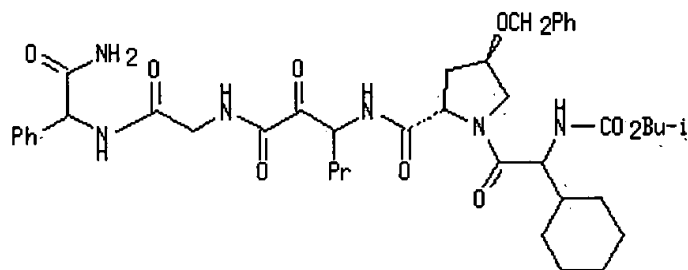
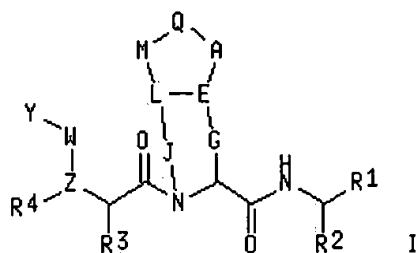


L24 ANSWER 2 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2003:912843 HCAPLUS
 DOCUMENT NUMBER: 139:381756
 TITLE: Preparation of peptides as NS3-serine protease inhibitors of hepatitis C virus
 INVENTOR(S): Saksena, Anil K.; Girijavallabhan, Viyyoor Moopil; Lovey, Raymond G.; Jao, Edwin; Bennett, Frank; McCormick, Jinping L.; Wang, Haiyan; Pike, Russell E.; Bogen, Stephane L.; Chan, Tin-Yau; Liu, Yi-tsung; Zhu, Zhaoning; Njoroge, F. George; Arasappan, Ashok; Parekh, Tejal; Ganguly, Ashit K.; Chen, Kevin X.; Venkatraman, Srikanth; Vaccaro, Henry A.; Pinto, Patrick A.; Santhanam, Bama; Kemp, Scott Jeffrey; Levy, Odile Esther; Lim-Wilby, Marguerita; Tamura, Susan Y.; Wu, Wanli; Hendrata, Siska; Huang, Yuhua
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 629 pp.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003216325	A1	20031120	US 2001-908955	20010719
<u>PRIORITY APPLN. INFO.:</u>			US 2001-908955	20010719
OTHER SOURCE(S):		MARPAT 139:381756		
GI				



II

AB The invention discloses novel peptides I [Y is alkyl, alkylaryl, heteroalkyl, heteroaryl, aryl- or alkylheteroaryl, cycloalkyl, alkyloxy, alkylaryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkylarylamino, arylamino, heteroarylamino, cycloalkylamino, or heterocycloalkylamino; R1 is acyl; Z is O, N, CH or CR; R, R2-R4 are H, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halo, (cycloalkyl)alkyl, or (heterocycloalkyl)alkyl; W, Q, G, J, L, M independently may be present or absent; W is CO, CS, C(:N-CN), or SO₂; Q is CH, N, P, alkylidene, O, NR, S, or SO₂; A is O, CH, alkylidene, NR, S, SO₂, or a bond; E is CH, N, alkylidene, or a double bond; G is alkylidene; J is alkylidene, SO₂, NH, NR, or O; L is CH, CR, O, S, or NR; M is O, NR, S, SO₂, or alkylidene (with provisos)] which have HCV protease inhibitory activity as well as methods for prepg. such compds. In another embodiment, the invention discloses pharmaceutical compns. comprising such compds. as well as methods of using them to treat disorders assocd. with the HCV protease. Thus, peptide II was prepd. by the solid-phase method and showed K_i = 1-100 nM (category A) in the HCV continuous assay.

IT **394723-07-0P**

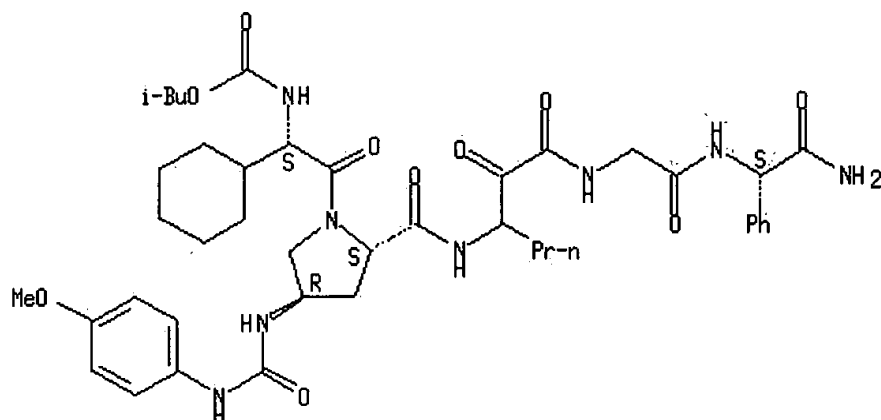
RL: IMF (Industrial manufacture); PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of peptides as NS3-serine protease inhibitors of hepatitis C virus)

RN **394723-07-0** HCAPLUS

CN Glycinamide, (2S)-2-cyclohexyl-N-[(2-methylpropoxy)carbonyl]glycyl-(4R)-4-[[[(4-methoxyphenyl)amino]carbonyl]amino]-L-prolyl-3-amino-2-oxohexanoylglycyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L24 ANSWER 3 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2003:892762 HCAPLUS
 DOCUMENT NUMBER: 139:395938
 TITLE: Preparation of ureas as positive allosteric modulators of the nicotinic acetylcholine receptor
 INVENTOR(S): Piotrowski, David W.; Rogers, Bruce N.; McWhorter, William W., Jr.; Walker, Daniel P.; Corbett, Jeffrey W.; Groppi, Vincent E., Jr.; Rudmann, Daniel G.
 PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, USA
 SOURCE: PCT Int. Appl., 159 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003093250	A2	20031113	WO 2003-US11493	20030428
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003236287	A1	20031225	US 2003-423062	20030425
PRIORITY APPLN. INFO.:			US 2002-377364P	P 20020503
			US 2003-456941P	P 20030324

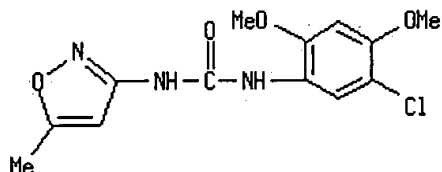
OTHER SOURCE(S): MARPAT 139:395938
 AB ANHCXNHB [X = O, S; A = (un)substituted Ph, 6-membered N heteroaryl; B = (un)substituted 5-6-membered heteroaryl] were prepd. to treat diseases or conditions in which the $\alpha 7$ nAChR is known to be involved (no data). Thus, 2,4-Me(MeO)C₆H₃NH₂ was treated with 3-F₃CC₆H₄CNO to give 2,4-Me(MeO)C₆H₃NHCONHC₆H₄CF₃-3.

IT 501925-31-1P

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of ureas as pos. allosteric modulators of the nicotinic

acetylcholine receptor)

RN 501925-31-1 HCAPLUS

CN Urea, N-(5-chloro-2,4-dimethoxyphenyl)-N'-(5-methyl-3-isoxazolyl)- (9CI)
(CA INDEX NAME)

L24 ANSWER 4 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2003:696868 HCAPLUS

DOCUMENT NUMBER: 139:230619

TITLE: Preparation of N-[1-(6-fluoronaphthalen-2-ylmethyl)pyrrolidin-3-yl]urea derivatives as CCR3 inhibitors

INVENTOR(S): Imaoka, Takayuki; Kawamura, Kuniaki; Kaneko, Masayuki; Kozono, Hideki; Morihira, Koichiro; Kubota, Hirokazu; Morokata, Tatsuaki; Kaneeda, Masanobu

PATENT ASSIGNEE(S): Toray Industries, Inc., Japan; Yamanouchi Pharmaceutical Co., Ltd.

SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

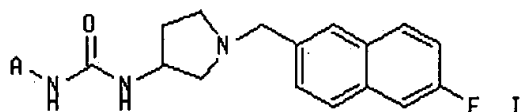
LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003072545	A1	20030904	WO 2003-JP2227	20030227
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:	JP 2002-51900	A	20020227
	JP 2003-20822	A	20030129

OTHER SOURCE(S): MARPAT 139:230619
GI

AB Cyclic amine compds. represented by the general formula (I) [wherein A is

a group which is selected from the group consisting of substituted aryls, substituted heterocyclic groups, and substituted cycloalkyls, has at least one substituent X, and may have at least one substituent Y (wherein the substituent X is selected from the group consisting of HO-(C1-6 alkyl), HO-(C2-6 alkyl)-O-(C1-6 alkyl), HO₂C-(C1-6 alkyl), (C1-6 alkyl)-OCO-(C1-6 alkyl), H₂NCO-(C1-6 alkyl), (C1-3 alkyl)NCO-(C1-6 alkyl), (C1-3 alkyl)-CONH-(C1-6 alkyl), HO₂C-(C1-6 alkyl)-O-(C1-6 alkyl), etc., and the substituent Y is selected from the group consisting of halogeno, C1-3 alkyl, OH, methoxy, CN, and CF₃) or pharmaceutically acceptable salts thereof are prepd. These compds. are C-C chemokine receptor 3 (CCR-3) inhibitors and useful for the treatment of inflammatory diseases, inflammatory cell infiltration, and diseases caused by eosinophil infiltration. They are excellent in oral absorbability. Thus, 3-[3-(tert-butyldimethylsilyloxy)propoxy]phenylamine was dissolved in MeCN, treated with NaHCO₃, cooled with ice, treated with 4-nitrophenyl chloroformate, stirred at room temp. for 1 h, cooled in ice, treated with (R)-1-[(6-fluoronaphthalen-2-yl)methyl]pyrrolidin-3-ylamine and Et₃N, stirred at room temp. overnight to give N-[3-[3-(tert-butyldimethylsilyloxy)propoxy]phenyl]-N'-[(R)-1-[(6-fluoronaphthalen-2-yl)methyl]pyrrolidin-3-yl]urea which was treated with Bu₄NF in THF at room temp. for 2 h to give 89% N-[3-(3-hydroxypropoxy)phenyl]-N'-[(R)-1-[(6-fluoronaphthalen-2-yl)methyl]pyrrolidin-3-yl]urea (II). II inhibited the human eotaxin-induced increase in cellular Ca²⁺ ion concn. in human CCR3-transformed B300-19 cell with IC₅₀ of 38 nM.

IT 592551-76-3P

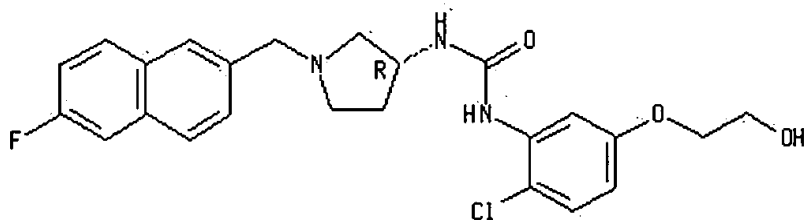
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of N-[(fluoronaphthalenylmethyl)pyrrolidinyl]urea derivs. as CCR3 inhibitors for treatment of inflammations, inflammatory cell infiltration, and diseases caused by eosinophil infiltration)

RN 592551-76-3 HCAPLUS

CN Urea, N-[2-chloro-5-(2-hydroxyethoxy)phenyl]-N'-[(3R)-1-[(6-fluoro-2-naphthalenyl)methyl]-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 5 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER:

2003:591204 HCAPLUS

DOCUMENT NUMBER:

139:149928

TITLE:

Preparation of peptides as NS3-serine protease inhibitors of hepatitis C virus

INVENTOR(S):

Saksena, Anil K.; Girijavallabh, Viyyoor M.; Lovey, Raymond G.; Jao, Edwin; Bennett, Frank; McCormick, Jinping L.; Wang, Haiyan; Pike, Russell E.; Bogen, Stephane L.; Chan, Tin-yau; Liu, Yi-tsung; Zhu, Zhaoning; Njoroge, George F.; Arasappan, Ashok;

Parekh, Tejal; Ganguly, Ashit K.; Chen, Kevin X.; Venkatraman, Srikanth; Vaccaro, Henry A.; Pinto, Patrick A.; Santhanam, Bama; Kemp, Scott Jeffrey; Levy, Odile Esther; Lim-Wilby, Marguerita; Tamura, Susan Y.; Wu, Wanli; Hendrata, Siska; Huang, Yuhua; Wong, Jesse K.; Nair, Latha G.

PATENT ASSIGNEE(S): Schering Corporation, USA; Corvas International, Inc.
SOURCE: PCT Int. Appl., 633 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

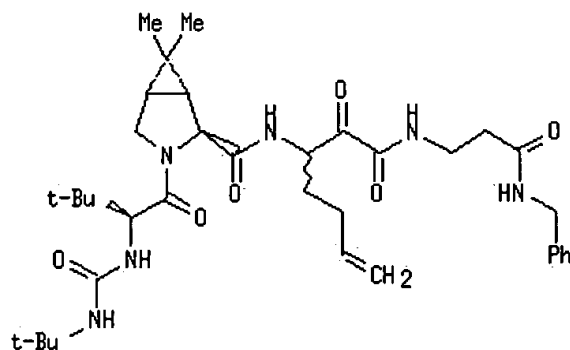
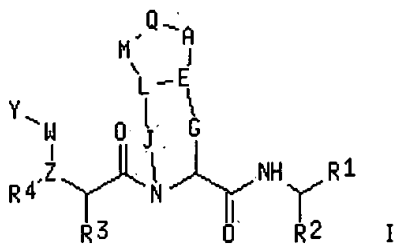
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003062265	A2	20030731	WO 2003-US1430	20030116
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2002-52386 A 20020118

OTHER SOURCE(S): MARPAT 139:149928

GI



AB The invention discloses novel peptides I [Y is alkyl, alkylaryl, heteroalkyl, heteroaryl, aryl- or alkylheteroaryl, cycloalkyl, alkyloxy, alkylaryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkylarylamino, arylamino, heteroarylamino,

cycloalkylamino, or heterocycloalkylamino; R1 is acyl; Z is selected from O, N, CH or CR; R, R2-R4 are H, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halo, (cycloalkyl)alkyl, or (heterocycloalkyl)alkyl; W, Q, G, J, L, M independently may be present or absent; W is CO, CS, C(:N-CN), or SO2; Q is CH, N, P, alkylidene, O, NR, S, or SO2; A is O, CH, alkylidene, NR, S, SO2, or a bond; E is CH, N, alkylidene, or a double bond; G is alkylidene; J is alkylidene, SO2, NH, NR, or O; L is CH, CR, O, S, or NR; M is O, NR, S, SO2, or alkylidene (with provisos)] which have HCV protease inhibitory activity as well as methods for prepg. such compds. In another embodiment, the invention discloses pharmaceutical compns. comprising such compds. as well as methods of using them to treat disorders assocd. with the HCV protease. Thus, peptide II was prepd. and showed $K_i = 1-100$ nM (category A) in the HCV continuous assay.

IT 394723-07-0P

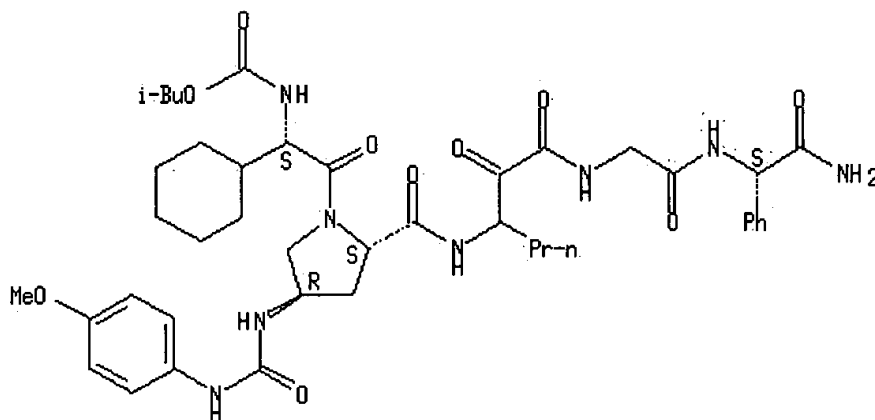
RL: IMF (Industrial manufacture); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of peptides as NS3-serine protease inhibitors of hepatitis C virus)

RN 394723-07-0 HCAPLUS

CN Glycinamide, (2S)-2-cyclohexyl-N-[(2-methylpropoxy)carbonyl]glycyl-(4R)-4-[[[(4-methoxyphenyl)amino]carbonyl]amino]-L-prolyl-3-amino-2-oxohexanoylglycyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L24 ANSWER 6 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER:

2003:454318 HCAPLUS

DOCUMENT NUMBER:

139:36450

TITLE:

Preparation of 4-[(piperidylalkyl)ureido]quinolines, 4-[(pyrrolidylalkyl)ureido]quinolines, and analogs as urotensin II receptor antagonists

INVENTOR(S):

Aissaoui, Hamed; Binkert, Christoph; Clozel, Martine; Mathys, Boris; Mueller, Claus; Nayler, Oliver; Scherz, Michael; Velker, Joerg; Weller, Thomas

PATENT ASSIGNEE(S):

Actelion Pharmaceuticals Ltd., Switz.

SOURCE:

PCT Int. Appl., 139 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

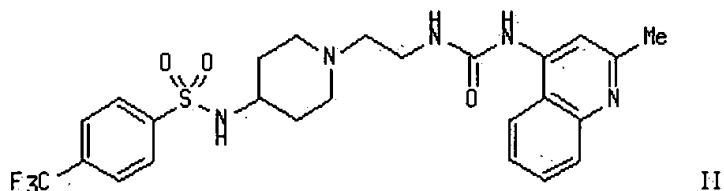
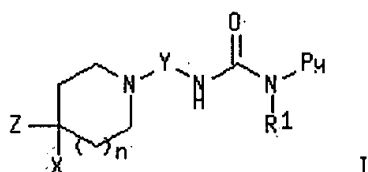
LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003048154	A1	20030612	WO 2002-EP13577	20021202
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.:			WO 2001-EP14195	A 20011204
OTHER SOURCE(S):			MARPAT 139:36450	
GI				



AB Title (pyridin-4-yl)urea derivs. and related compds. I [wherein Py = (un)substituted 2-NR₂R₃-pyridin-4-yl, quinolin-4-yl, (5,6,7,8-tetrahydro)[1,8]naphthyridin-4-yl, or 2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-4-yl; X = aryl(oxy), arylalkyl, (aryl)alkyl-SO₂NR₂, aryl-SO₂NR₂, (aryl)alkyl-CONR₂, aryl-CONR₂, (aryl)alkyl-NR₃CONR₂, aryl-NR₃CONR₂, aroyl, arylalkanoyl, (aryl)alkyl-NR₂CO, aryl-NR₂CO, etc.; Y = CR₄R₅(CH₂)_m or (CH₂)_mCR₄R₅; Z = H; or when X = aryl(alkyl), Z = H, OH, CO₂H, aryl-CONR₂, alkyl-NR₂CO, or (aryl)alkyl-NR₂CO; m = 1-2; n = 0-1; R₁ = H or alkyl; R₂ and R₃ = independently H or (aryl)alkyl; or NR₂R₃ = piperidyl, pyrrolidinyl, or morpholinyl; R₄ = H, (aryl)alkyl, or aryl; R₅ = H or Me; or CR₄R₅ = carbocyclyl; and enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, solvates, or morphol. forms thereof] were prepd. as urotensin II receptor antagonists. For example, reaction of 4-amino-2-methylquinoline with 2-chloroethylisocyanate gave the urea. Substitution with piperidin-4-ylcarbamic acid tert-Bu ester, deprotection of the amine, and coupling with 4-trifluoromethylbenzenesulfonyl chloride provided II. Compds. of the invention inhibited binding of human [125I]-urotensin II to human-derived rhabdomyosarcoma cells in vitro with IC₅₀ values ranging from 0.1 nM to 1000 nM. Thus, I are useful as active ingredients in pharmaceutical compns. for the treatment of vasoconstriction, proliferation, and a wide variety of other disease states assocd. with urotensin II regulation (no data).

IT **540767-32-6P**, 1-(2-Methylquinolin-4-yl)-3-[2-[3-[3-(4-phenoxyphenyl)ureido]pyrrolidin-1-yl]ethyl]urea

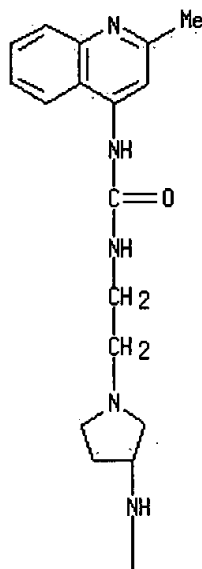
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU** (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(urotensin antagonist; prepn. of ureidoquinolines and analogs as urotensin II receptor antagonists for treatment of vasoconstriction, proliferation, and other disorders)

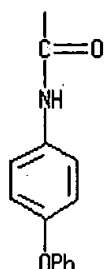
RN **540767-32-6** HCAPLUS

CN Urea, N-[1-[2-[[[(2-methyl-4-quinolinyl)amino]carbonyl]amino]ethyl]-3-pyrrolidinyl]-N'-(4-phenoxyphenyl)-(9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 7 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2003:434550 HCAPLUS

DOCUMENT NUMBER: 139:22112

TITLE: Preparation of ureido and related piperidines as CCR3 receptor antagonists for treating asthma

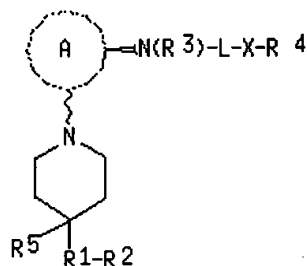
INVENTOR(S): Du Bois, Daisy Joe; Kertesz, Denis John; Sjogren, Eric Brian; Smith, David Bernard; Wang, Bei Han

PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.

SOURCE: PCT Int. Appl., 93 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003045937	A1	20030605	WO 2002-EP13218	20021125
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003229121	A1	20031211	US 2002-307130	20021129
<u>PRIORITY APPLN. INFO.:</u>				
			US 2001-334653P	P 20011130
			US 2001-334655P	P 20011130
			US 2001-334819P	P 20011130

OTHER SOURCE(S): MARPAT 139:22112
 GI



AB The present invention relates to N-ureido-piperidines (shown as I; variables defined below; e.g. trans-1-[2-[4-(4-chlorobenzyl)piperidin-1-yl]cyclohexyl]-3-(3,4,5-trimethoxyphenyl)urea). The compds. are useful as CCR3 receptor antagonists by blocking the ability of the CCR-3 receptor to bind RANTES, MCP-3 and eotaxin and thereby preventing the recruitment of eosinophils, and therefore, may be used for treatment of CCR3 mediated diseases such as asthma. Five pharmaceutical formulations are described. Seven example preps. of intermediates and 31 of I are included. For example, trans-1-[2-[4-(4-chlorobenzyl)piperidin-1-yl]cyclohexyl]-3-(3,4,5-trimethoxyphenyl)urea was prepd. in 55% yield from [trans-2-[4-(4-chlorobenzyl)piperidin-1-yl]cyclohexyl]amine (56 mg, 0.18 mmol) and 5-isocyanato-1,2,3-trimethoxybenzene in CH₂Cl₂; [trans-2-[4-(4-chlorobenzyl)piperidin-1-yl]cyclohexyl]amine was prepd. in 2 steps starting from 4-(4-chlorobenzyl)piperidine and 7-oxabicyclo[4.1.0]heptane via intermediate trans-2-[4-(4-chlorobenzyl)piperidin-1-yl]cyclohexanol with yields of 88 and 67%. IC₅₀ values for inhibiting the binding of 125I eotaxin to CCR-3 L1.2 transfectant cells were detd. for 10 examples of I, e.g. 0.0185 μM for trans-N-[3-[3-[2-[4-(4-Chlorobenzyl)piperidin-1-yl]cyclopentyl]ureido]phenyl]acetamide. For I: R1 is (C1-C2)alkylene; R2

is (un)substituted phenyl; R3 is H, C1-6 alkyl, acyl, aryl, or aryl C1-6 alkyl; ring A is a C3-7 cycloalkyl, heterocyclyl, or (un)substituted phenyl; L is -C(O)-, -C(S)-, -SO2-, -C(O)N(Ra)-, -C(S)N(Ra)-, -SO2N(Ra)-, -C(O)O-, -C(S)-O-, -S(O)2O-; where Ra is H, C1-6 alkyl, acyl, aryl, aryl C1-6 alkyl, C1-6 alkoxy carbonyl, or benzyloxy carbonyl; X is absent, -(CR'R'')O-, -(CR'R'')S-, -(CR'R'')NRb- or C1-6 alkylene; where R' and R'' = H or C1-6 alkyl, and Rb is H or C1-6 alkyl; R4 is aryl or heteroaryl; and R5 is H or C1-6 alkyl; provided that when R1 is -CH2-, R2 is Ph, R3 is H, R5 is H, A is Ph, L is -C(O)NH- and X is absent, then R4 is not 2,5-difluorophenyl.

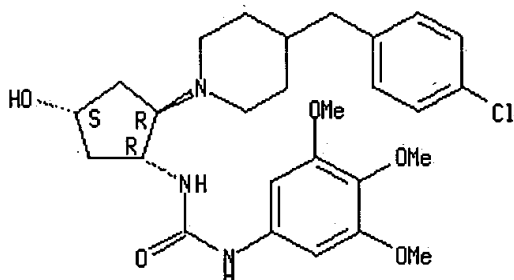
IT **538371-04-9P**, (\pm)-1-[(1R,2R,4S)-2-[4-(4-Chlorobenzyl)piperidin-1-yl]-4-hydroxycyclopentyl]-3-(3,4,5-trimethoxyphenyl)urea
 RL: DGN (Diagnostic use); PAC (Pharmacological activity); RCT (Reactant); **THU (Therapeutic use)**; THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(drug candidate and diagnosis agent; prepn. of ureido and related piperidines as CCR3 receptor antagonists for treating asthma)

RN **538371-04-9** HCAPLUS

CN Urea, N-[(1R,2R,4S)-2-[4-[(4-chlorophenyl)methyl]-1-piperidinyl]-4-hydroxycyclopentyl]-N'-(3,4,5-trimethoxyphenyl)-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 8 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2003:434371 HCAPLUS

DOCUMENT NUMBER: 139:22109

TITLE: Preparation of piperazinyl carboxamides, sulfonamides, ureas and related compounds as CCR3 receptor antagonists for treating asthma

INVENTOR(S): Du Bois, Daisy Joe; Kertesz, Denis John; Sjogren, Eric Brian; Smith, David Bernard; Wang, Bei Han

PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.

SOURCE: PCT Int. Appl., 59 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003045393	A1	20030605	WO 2002-EP13217	20021125
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
 GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
 LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
 PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
 UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
 CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
 PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
 NE, SN, TD, TG

US 2003176441 A1 20030918

US 2002-307159 20021129

US 2003229121 A1 20031211

US 2002-307130 20021129

PRIORITY APPLN. INFO.:

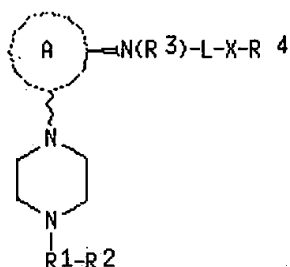
US 2001-334655P P 20011130

US 2001-334653P P 20011130

US 2001-334819P P 20011130

OTHER SOURCE(S): MARPAT 139:22109

GI



AB The present invention relates to piperazinyl carboxamides, sulfonamides, ureas and related compds. (shown as I; variables defined below; e.g. trans-1-[4-[4-(4-chlorobenzyl)piperazin-1-yl]tetrahydrofuran-3-yl]-3-(3,4,5-trimethoxyphenyl)urea dihydrochloride). The compds. are useful as CCR3 receptor antagonists by blocking the ability of the CCR-3 receptor to bind RANTES, MCP-3 and eotaxin and thereby preventing the recruitment of eosinophils, and therefore, may be used for treatment of CCR3 mediated diseases such as asthma or for diagnosis. Five pharmaceutical formulations are described. Seven example preps. of I are included. For example, the above compd. was prepd. in 77% yield from trans-4-[4-(4-chlorobenzyl)piperazin-1-yl]tetrahydrofuran-3-ylamine (0.41 mmol) and 5-isocyanato-1,2,3-trimethoxybenzene (0.50 mmol) in CH₂Cl₂; prepn. of the amine is also described. IC₅₀ values for inhibiting the binding of ¹²⁵I eotaxin to CCR-3 L1.2 transfectant cells were detd. for 4 examples of I, e.g. 0.1099 μM for the above example. For I: R₁ is (C₁-C₂)alkylene; R₂ is (un)substituted phenyl; R₃ is H, C₁-6 alkyl, acyl, aryl, or aryl C₁-6-alkyl; ring A is a C₃-7 cycloalkyl, heterocyclyl, or (un)substituted phenyl; L is -C(O)-, -C(S)-, -SO₂-, -C(O)N(Ra)-, -C(S)N(Ra)-, -SO₂N(Ra)-, -C(O)O-, -C(S)O-, -S(O)O₂-; where Ra is H, C₁-6 alkyl, acyl, aryl, aryl C₁-6 alkyl, C₁-6-alkoxycarbonyl, or benzyloxycarbonyl. X is absent, -(CR'R'')O-, -(CR'R'')S-, -(CR'R'')NRb- or C₁-6 alkylene; where R' and R'' = H or C₁-6-alkyl, and Rb is H or C₁-6 alkyl; R₄ is aryl or heteroaryl; provided that I is not 1-[2-[4-(3,4-dichlorobenzyl)piperazin-1-yl]cyclohexyl]-3-(3-methoxyphenyl)urea; and provided that when ring A is Ph or cyclohexyl, then R₂ is substituted Ph.

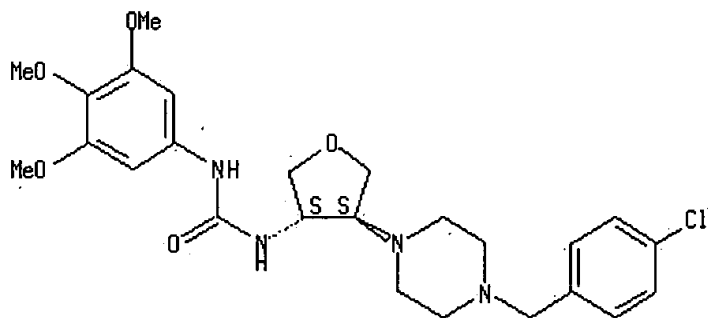
IT **538342-64-2P**, trans-1-[4-[4-(4-Chlorobenzyl)piperazin-1-yl]tetrahydrofuran-3-yl]-3-(3,4,5-trimethoxyphenyl)urea dihydrochloride
 RL: DGN (Diagnostic use); PAC (Pharmacological activity); SPN (Synthetic

preparation); THU (Therapeutic use); BIOL (Biological study);
 PREP (Preparation); USES (Uses)
 (drug candidate; prepn. of piperazinyl carboxamides, sulfonamides,
 ureas and related compds. as CCR3 receptor antagonists for
 treating/diagnosing asthma)

RN 538342-64-2 HCAPLUS

CN Urea, N-[(3R,4R)-4-[4-[(4-chlorophenyl)methyl]-1-piperazinyl]tetrahydro-3-furanyl]-N'-(3,4,5-trimethoxyphenyl)-, dihydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



2 HCl

REFERENCE COUNT:

3

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 9 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2003:282524 HCAPLUS

DOCUMENT NUMBER: 138:304064

TITLE: Preparation of phenylurea derivatives as vanilloid
 receptor agonists

INVENTOR(S): Matsumoto, Takahiro; Yamamoto, Masataka; Nagabukuro,
 Hiroshi; Mochizuki, Manabu

PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan

SOURCE: PCT Int. Appl., 293 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

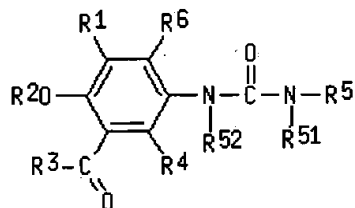
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003029199	A1	20030410	WO 2002-JP9995	20020927
WO 2003029199	C2	20030925		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
 CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
 GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS,
 LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,
 PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
 UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
 TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
 CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,

PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 2001-300564 A 20010928
OTHER SOURCE(S): MARPAT 138:304064
GI



I

AB The title compds. I [R1, R4 and R6 are each independently hydrogen, halogeno, or hydrocarbyl; R2 is hydrocarbyl or a heterocyclic group; R3 is hydrocarbyl, etc.; R5 is hydrocarbyl or a heterocyclic group (except quinolyl) and R51 is hydrogen or hydrocarbyl, or R5 and R51 together with the nitrogen atom adjacent thereto may form a ring; and R52 is hydrogen or hydrocarbyl] are prepd. I are useful for the treatment of pain, urinary incontinence, etc. In a tail flick test using mice, one compd. of this invention showed a min. ED of 1 mg/kg.

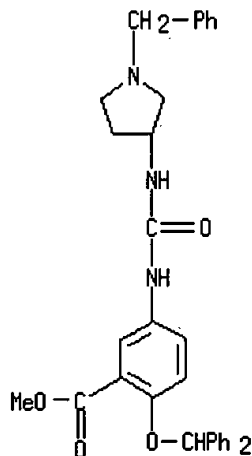
IT 508214-27-5P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of phenylurea derivs. as vanilloid receptor agonists)

RN 508214-27-5 HCAPLUS

CN Benzoic acid, 2-(diphenylmethoxy)-5-[[[1-(phenylmethyl)-3-pyrrolidinyl]amino]carbonyl]amino]-, methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 10 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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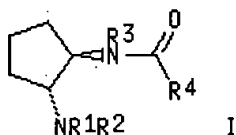
ACCESSION NUMBER: 2003:221645 HCAPLUS

DOCUMENT NUMBER: 138:254963

TITLE: Preparation of acylaminocyclopentaneamines as CCR-3 chemokine receptor antagonists that inhibit eosinophilic recruitment by chemokines.

INVENTOR(S): Du Bois, Daisy Joe
 PATENT ASSIGNEE(S): F. Hoffmann-La Roche AG, Switz.
 SOURCE: PCT Int. Appl., 51 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
<u>WO 2003022799</u>	A1	20030320	<u>WO 2002-EP9934</u>	20020905
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
<u>US 2003119885</u>	A1	20030626	<u>US 2002-242610</u>	20020912
<u>PRIORITY APPLN. INFO.:</u>			<u>US 2001-318992P</u>	P 20010913
<u>OTHER SOURCE(S):</u>		MARPAT 138:254963		
GI				



AB Title compds. [I; R1 = H, alkyl; R2 = aralkyl; R3 = H, alkyl, acyl, aryl, aralkyl; R4 = WXYZ; W = null, alkylene; X = null, CO, O, S, SO, SO₂, NRa; Ra = H, alkyl, acyl, aryl, aralkyl, alkoxycarbonyl, benzyloxycarbonyl; Y = arylene, heteroarylene; Z = H, aryl, heteroaryl, aryloxy, heteroaryloxy, aralkyl, heteroaralkyl], were prepd. Thus, reaction of trans-N-[2-(4-chlorophenyl)ethyl]-N-methylcyclopentane-1,2-diamine and 5-isocyanato-1,2,3-trimethoxybenzene reacted to give trans-1-[2-[[2-(4-chlorophenyl)ethyl]methylamino]cyclopentyl]-3-(3,4,5-trimethoxyphenyl)urea hydrochloride. The latter inhibited [125I]eotaxin binding to CCR-3 L1.2 transfectant cells with IC₅₀ = 5.4 μM.

IT **502522-59-0P**

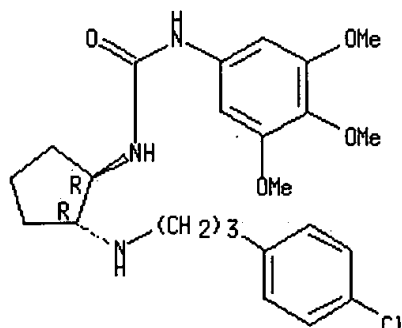
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU** (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of acylaminocyclopentaneamines as CCR-3 receptor antagonists that inhibit eosinophilic recruitment by chemokines)

RN 502522-59-0 HCAPLUS

CN Urea, N-[(1R,2R)-2-[[3-(4-chlorophenyl)propyl]amino]cyclopentyl]-N'-(3,4,5-trimethoxyphenyl)-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 3

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 11 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2002:444499 HCAPLUS

DOCUMENT NUMBER: 137:33207

TITLE: Preparation of novel N-substituted- γ,γ -
trisubstituted lactam derivatives as matrix
metalloproteinase inhibitorsINVENTOR(S): Duan, Jingwu; DeCicco, Carl P.; Wasserman, Zelda R.;
Maduskuie, Thomas P., Jr.

PATENT ASSIGNEE(S): USA

SOURCE: U.S., 119 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

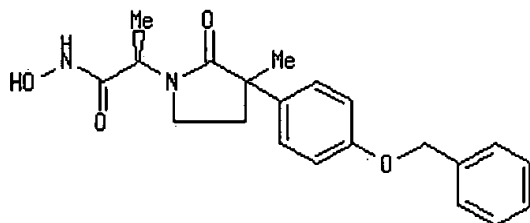
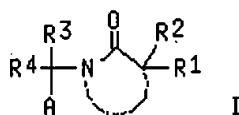
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6403632	B1	20020611	US 2000-516709	20000301
US 2003134827	A1	20030717	US 2002-96619	20020312
US 6610731	B2	20030826		

<u>PRIORITY APPLN. INFO.:</u>	<u>US 1997-62418P</u>	P	19971003
	<u>US 1998-165747</u>	A3	19981002
	<u>US 2000-516709</u>	A3	20000301

OTHER SOURCE(S): MARPAT 137:33207

GI



AB Title compds. [I; A is selected from COOH, CH₂COOH, CONHOH, SH, CH₂SH, PO(OH)₂, etc.; ring B is a 4-8 membered cyclic amide contg. 0-3 heteroatoms from O, N, and S, etc.; R₁ is phenylmethoxyphenyl, phenoxyphenyl, etc.; R₂ is H, CH₃, Et, i-Pr, etc.; R₁-R₂ combine to form heterocyclic; R₃ is H, alkylene, heterocyclic, etc.; R₄ is H, alkylene, etc.; R₃-R₄ combine to form heterocyclic], stereoisomer, and pharmaceutically acceptable salt thereof are prepd. as useful metalloprotease inhibitors. For instance, 4-benzyloxyphenyl acetate was sequentially alkylated (THF, NaHMS) with MeI and allyl bromide to afford the α,α-bis(alkylated) deriv. which was converted to the aldehyde (CH₂Cl₂, O₃) and was subsequently reacted with D-alanine Me ester hydrochloride and Zn⁰ in HOAc to yield the lactam ester. This intermediate was treated with hydroxylamine to give hydroxamic acid II.

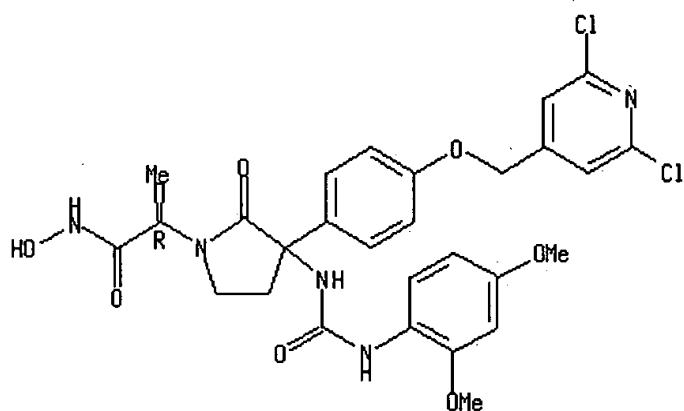
IT **223403-48-3P**, 1-Pyrrolidineacetamide, 3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-3-[[[(2,4-dimethoxyphenyl)amino]carbonyl]amino]-N-hydroxy-α-methyl-2-oxo-, (αR)-
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU** (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(N-γ,γ-trisubstituted lactam derivs. as MMP-3/aggreacanase inhibitors)

RN **223403-48-3** HCAPLUS

CN 1-Pyrrolidineacetamide, 3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-3-[[[(2,4-dimethoxyphenyl)amino]carbonyl]amino]-N-hydroxy-α-methyl-2-oxo-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

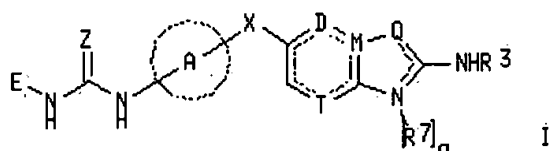
L24 ANSWER 12 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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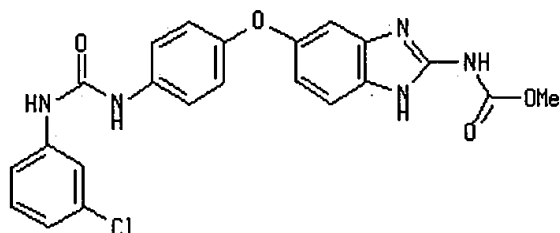
ACCESSION NUMBER: 2002:428885 HCAPLUS
DOCUMENT NUMBER: 137:6179
TITLE: Preparation of benzimidazoles as TIE-2 and/or VEGFR2 inhibitors
INVENTOR(S): Cheung, Mui; Harris, Philip Anthony; Hasegawa, Masaichi; Ida, Satoru; Kano, Kazuya; Nishigaki, Naohiko; Sato, Hideyuki; Veal, James Martin; Washio, Yoshiaki; West, Rob I.
PATENT ASSIGNEE(S): Glaxo Group Limited, UK; Glaxosmithkline K.K.
SOURCE: PCT Int. Appl., 217 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002044156	A2	20020606	WO 2001-US44553	20011128
WO 2002044156	A3	20021017		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002032439	A5	20020611	AU 2002-32439	20011128
EP 1341771	A2	20030910	EP 2001-991963	20011128
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRIORITY APPLN. INFO.:				
			US 2000-253868P	P 20001129
			US 2001-310939P	P 20010808
			WO 2001-US44553	W 20011128

OTHER SOURCE(S): MARPAT 137:6179
GI



I



II

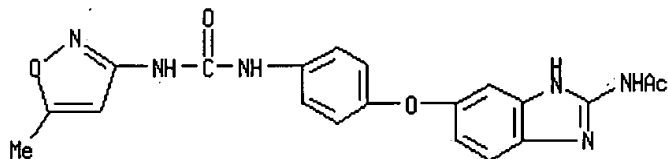
AB The title compds. [I; E = (un)substituted aryl, heteroaryl; A = aryl, heteroaryl, heterocyclyl; X = S, O, SO₂, SO, CH₂, CHOH, CO; Z = O, S; p = 0-1; q = 0-1; D = CH, T = CR₈, M = C and Q = NT₇p, wherein p = 0 and q = 1; or D = CH, T = CR₈, M = C and Q = NR₇p, wherein p = 1 and q = 0, or D = CH, T = CR₈, M = C and Q = S or O, wherein q = 0; or D = N, T = CR₈, M = C and Q = NR₇p, wherein either p or q = 0 and the other = 1; or D = CH, T = N, M = C and Q = NR₇p, wherein either p or q = 0 and the other = 1; or D = CH, T = CR₈, M = N and Q = CH, wherein q = 0; R₁ = alkyl, haloalkyl, aryl, etc.; R₂ = H, alkyl, aryl, etc.; R₃ = alkylene or alkylene substituted by oxo, and is linked together with N atom to which it is attached and to one of the benzimidazole N atoms to form a heterocyclic compd. fused to the benzimidazole; R₇ = H, alkyl, etc.; R₈ = H, halo] and their salts, useful in the treatment of hyperproliferative diseases, were prepd. Thus, reacting Me [5-(4-aminophenoxy)-1H-benzimidazol-2-yl]carbamate (prepn. given) with 3-chlorophenyl isocyanate in THF afforded 69% II which showed pIC₅₀ of > 7.0 in TIE-2 and VEGFR2 enzyme assays.

IT 433225-41-3P

RL: CPN (Combinatorial preparation); PAC (Pharmacological activity);
THU (Therapeutic use); BIOL (Biological study); CMBI
 (Combinatorial study); PREP (Preparation); USES (Uses)
 (prepn. of benzimidazoles as TIE-2 and/or VEGFR2 inhibitors)

RN 433225-41-3 HCAPLUS

CN Acetamide, N-[5-[4-[[[(5-methyl-3-isoxazolyl)amino]carbonyl]amino]phenoxy]-1H-benzimidazol-2-yl]- (9CI) (CA INDEX NAME)



L24 ANSWER 13 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2002:90074 HCAPLUS

DOCUMENT NUMBER: 136:151440

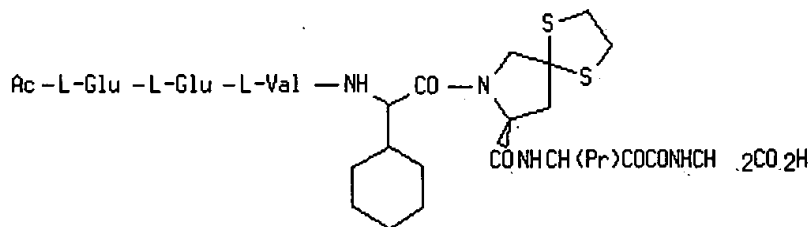
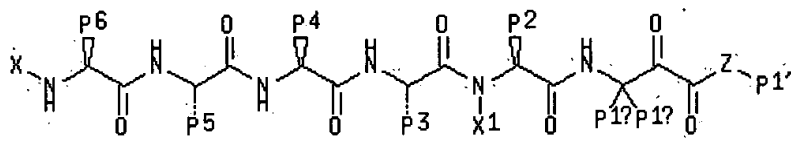
TITLE: Preparation of novel peptides as NS3-serine protease inhibitors of hepatitis C virus

INVENTOR(S): Saksena, Anil K.; Girjavallabhan, Viyyoor Moopil; Lovey, Raymond G.; Jao, Edwin E.; Bennett, Frank; McCormick, Jinping; Wang, Haiyan; Pike, Russell E.; Bogen, Stephane L.; Liu, Yi-Tsung; Arasappan, Ashok;

	Parekh, Tejal; Pinto, Patrick A.; Njoroge, F. George; Ganguly, Ashit K.; Brunck, Terence K.; Kemp, Scott Jeffrey; Levy, Odile Esther; Lim-Wilby, Marguerita Schering Corporation, USA; Corvas International, Inc.
PATENT ASSIGNEE(S):	
SOURCE:	PCT Int. Appl., 197 pp.
	CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002008256	A2	20020131	WO 2001-US22826	20010719
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
US 2003036501	A1	20030220	US 2001-909062	20010719
EP 1301528	A2	20030416	EP 2001-959046	20010719
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
PRIORITY APPLN. INFO.:			US 2000-220109P	P 20000721
			WO 2001-US22826	W 20010719

OTHER SOURCE(S) : MARPAT 136:151440
GI



AB Novel peptides I [Z = O, NH or substituted imino; X = (un)substituted alkylsulfonyl, heterocyclisulfonyl, heterocyclisulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylcarbonyl, heterocyclisulfonyl, heterocyclisulfonyl, arylcarbonyl, heteroarylcarbonyl, alkoxy carbonyl, heterocyclisulfonyl, aryloxy carbonyl, heteroaryloxy carbonyl, alkyaminocarbonyl, heterocyclisulfonyl, arylaminocarbonyl, or heteroarylamino carbonyl; X1 = H, alkyl, arylmethyl; P1a, P1b, P2-P6 = H, (un)substituted alkyl, alkenyl, cycloalkyl,

heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl; P1a and P1b may optionally be joined to each other to form a spirocyclic or spiroheterocyclic ring contg. 0-6 oxygen, nitrogen, sulfur, or phosphorus atoms; P1' = H, (un)substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl] having HCV protease inhibitory activity are disclosed. Thus, peptide II was prepd. via peptide coupling in soln. and showed $K_i = 1-100$ nM for inhibition of HCV protease.

IT 393523-09-6P

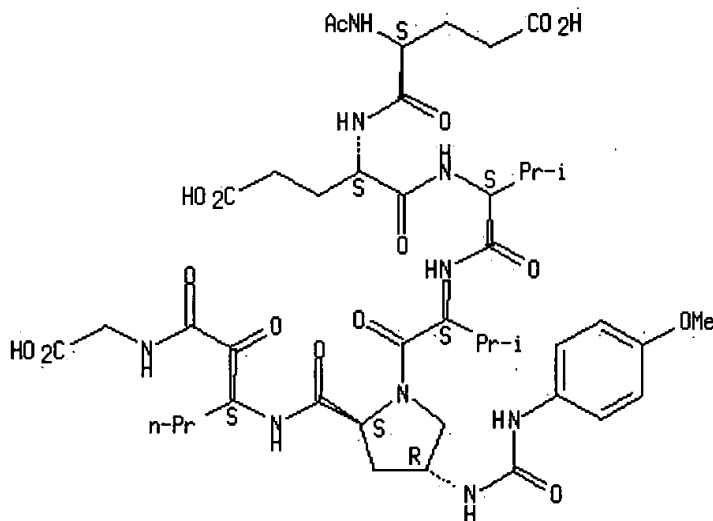
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of novel peptides as NS3-serine protease inhibitors of hepatitis C virus)

RN 393523-09-6 HCAPLUS

CN Glycine, N-acetyl-L- α -glutamyl-L- α -glutamyl-L-valyl-L-valyl-(4R)-4-[[[(4-methoxyphenyl)amino]carbonyl]amino]-L-prolyl-(3S)-3-amino-2-oxohexanoyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L24 ANSWER 14 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2002:90062 HCAPLUS

DOCUMENT NUMBER: 136:167698

TITLE: Preparation of peptides as NS3-serine protease inhibitors of hepatitis C virus

INVENTOR(S): Saksena, Anil K.; Girijavallabhan, Viyyoor Moopil; Lovey, Raymond G.; Jao, Edwin E.; Bennett, Frank; McCormick, Jinping L.; Wang, Haiyan; Pike, Russell E.; Bogen, Stephane L.; Chan, Tin-Yau; Liu, Yi-Tsung; Zhu, Zhaoning; Njoroge, F. George; Arasappan, Ashok; Parekh, Tejal N.; Ganguly, Ashit K.; Chen, Kevin X.; Venkatraman, Srikanth; Vaccaro, Henry A.; Pinto, Patrick A.; Santhanam, Bama; Wu, Wanli; Hendrata, Siska; Huang, Yuhua; Kemp, Scott Jeffrey; Levy, Odile Esther; Lim-Wilby, Marguerita; Tamura, Susan Y.

PATENT ASSIGNEE(S): Schering Corporation, USA; Corvas International, Inc.

SOURCE: PCT Int. Appl., 536 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002008244	A2	20020131	WO 2001-US22678	20010719
WO 2002008244	A3	20030619		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001076988	A5	20020205	AU 2001-76988	20010719
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BR 2001012540	A	20030624	BR 2001-12540	20010719
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EP 1385870	A2	20040204	EP 2001-954764	20010719
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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

JP 2004504404	T2	20040212	JP 2002-514149	20010719
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NO 2003000272	A	20030321	NO 2003-272	20030120
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PRIORITY APPLN. INFO.:

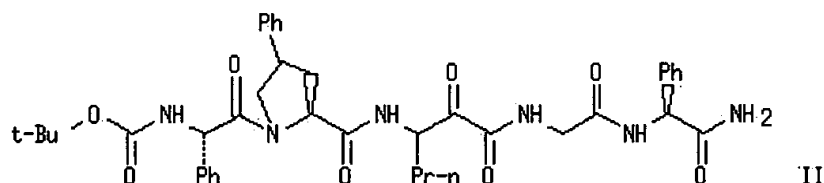
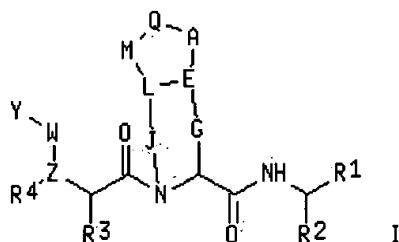
US 2000-220108P	P	20000721
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WO 2001-US22678	W	20010719
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OTHER SOURCE(S):

MARPAT 136:167698

GI



AB Peptides I were prepd. wherein Y is alkyl, alkyl-aryl, heteroaryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkylheteroaryl, cycloalkyl, alkyloxy, alkylaryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy,, alkylamino, arylamino, alkylarylamino, arylamino, heteroarylamino, cycloalkylamino and heterocycloalkylamino; R1 is acyl, borate; Z is selected from O, N, CH or CR; W, Q, G, J, L, M independently maybe present or absent; W is C=O, C=S, C(=N-CN), or SO; Q is CH, N, P, alkylidene, O, amine,S, or SO; A is O, CH, alkylidene, amine, S, SO or bond; E is CH, N, alkylidene, or double bond; G is alkylidene; J is

alkylidene, SO, NH, NR, O; L is CH, alkylidene, O, S or NR; M is O, NR, S, SO, alkylidene; p is 0 to 6; and R-R4 are independently selected from the group consisting of H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen; (cycloalkyl)alkyl and (heterocycloalkyl)alkyl, which have HCV protease inhibitory activity as well as methods for prepg. such compds. In another embodiment, the invention discloses pharmaceutical compns. comprising such compds. as well as methods of using them to treat disorders assocd. with the HCV protease. Thus peptide II was prepd. and tested as antiviral agent and NS3-serine protease inhibitors of hepatitis C virus with Ki ranges in category A = 1-100 nM; category B = 101-1,000 nM; category C > 1000 nM. Also disclosed is the use of I for the manuf. of a medicament for treating HCV, AIDS, and related disorders.

IT **394723-07-0P**

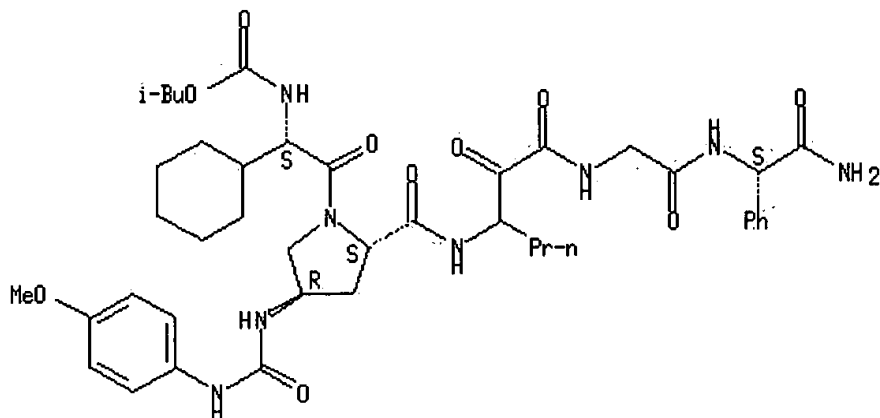
RL: IMF (Industrial manufacture); PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of peptides as NS3-serine protease inhibitors of hepatitis C virus)

RN **394723-07-0** HCAPLUS

CN Glycinamide, (2S)-2-cyclohexyl-N-[(2-methylpropoxy)carbonyl]glycyl-(4R)-4-[[[(4-methoxyphenyl)amino]carbonyl]amino]-L-prolyl-3-amino-2-oxohexanoylglycyl-2-phenyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L24 ANSWER 15 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER:

2001:923806 HCAPLUS

DOCUMENT NUMBER:

136:53742

TITLE:

Preparation of 5H-isoxazolo[4,3-c]quinolin-4-ones as MRP1 inhibitors

INVENTOR(S):

Lander, Peter Ambrose; Wang, Qiuping; Vepachedu, Sreenivasarao

PATENT ASSIGNEE(S):

Eli Lilly and Company, USA

SOURCE:

PCT Int. Appl., 54 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.

KIND DATE

APPLICATION NO. DATE

WO 2001096346	A1	20011220	WO 2001-US16475	20010531
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1301518	A1	20030416	EP 2001-941546	20010531
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003216425	A1	20031120	US 2003-296481	20030416
US 6673809	B2	20040106		

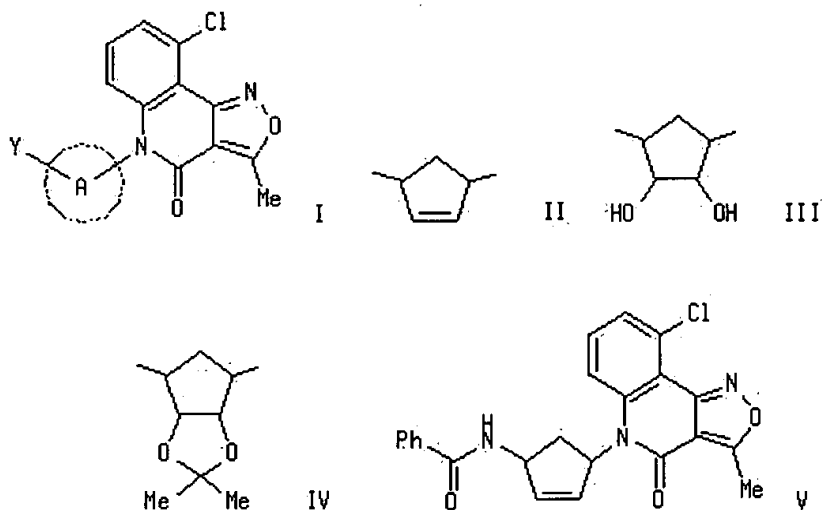
PRIORITY APPLN. INFO.:

US 2000-211430P P 20000614

WO 2001-US16475 W 20010531

OTHER SOURCE(S): MARPAT 136:53742

GI



AB The title compds. [I; A = II-IV; Y = ECOR1; ENR2R3; E = a bond, CH2; R1 = H, alkyl, cycloalkyl, etc.; R2 = H, alkyl, alkylaryl, aryl; R3 = H, alkyl, alkoxy, etc.], useful for inhibiting resistant neoplasms where the resistance is conferred in part or in total by MRP1 (no data), were prepd. Thus, reacting 5-(4-aminocyclopent-2-enyl)-9-chloro-3-methyl-5H-isoxazolo[4,3-c]quinolin-4-one (prepn. given) with benzoyl chloride in the presence of Et3N in CH2Cl2 afforded 55% V.

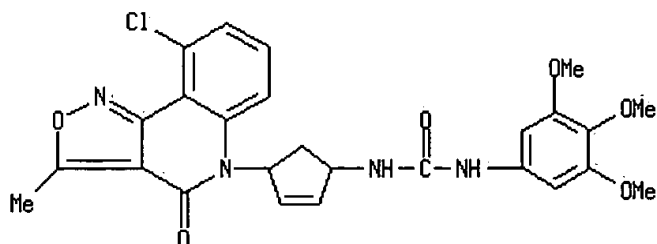
IT **381688-83-1P**

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of 5H-isoxazolo[4,3-c]quinolin-4-ones as MRP1 inhibitors)

RN **381688-83-1** HCAPLUS

CN Urea, N-[4-(9-chloro-3-methyl-4-oxoisoxazolo[4,3-c]quinolin-5(4H)-yl)-2-cyclopenten-1-yl]-N'-(3,4,5-trimethoxyphenyl)-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 16 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

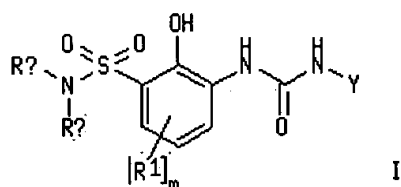
Full Text | Citing References

ACCESSION NUMBER: 2001:693247 HCAPLUS
 DOCUMENT NUMBER: 135:257156
 TITLE: Preparation of sulfonamido substituted phenyl heteroaryl ureas as IL-8 receptor antagonists
 INVENTOR(S): Widdowson, Katherine L.; Jin, Qi
 PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
 SOURCE: PCT Int. Appl., 44 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001068568	A2	20010920	WO 2001-US7746	20010309
WO 2001068568	A3	20020321		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001045606	A5	20010924	AU 2001-45606	20010309
EP 1261336	A2	20021204	EP 2001-918542	20010309
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003535820	T2	20031202	JP 2001-567669	20010309
NO 2002004193	A	20020903	NO 2002-4193	20020903
US 2003055286	A1	20030320	US 2002-220772	20020905
US 6608077	B2	20030819		

PRIORITY APPLN. INFO.: US 2000-188410P P 20000310
 WO 2001-US7746 W 20010309

OTHER SOURCE(S): MARPAT 135:257156
 GI



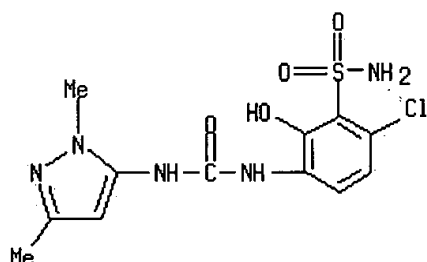
AB The title compds. [I; Rb = H, OH, aryl, etc.; m = 1-3; R1 = H, halo, NO2, etc.; Y = furyl, thiophenyl, pyridyl, etc.], useful in the treatment of disease states mediated by the chemokine, Interleukin-8 (IL-8), were prepd. Thus, reacting 3-amino-6-chloro-2-hydroxybenzenesulfonamide with 2-(azidocarbonyl)pyridine (prepn. given) in DMF afforded 62% I [Rb = H; R1 = 4-Cl; Y = 2-pyridyl]. The IL-8, and GRO- α chemokine effects of compds. I were detd. by in vitro assay (IC50 < 30 μ M).

IT **361392-27-0P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of sulfonamido substituted Ph heteroaryl ureas as IL-8 receptor antagonists)

RN 361392-27-0 HCAPLUS

CN Benzenesulfonamide, 6-chloro-3-[[[(1,3-dimethyl-1H-pyrazol-5-yl)amino]carbonyl]amino]-2-hydroxy- (9CI) (CA INDEX NAME)



L24 ANSWER 17 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2001:693081 HCAPLUS
DOCUMENT NUMBER: 135:257046
TITLE: Preparation of sulfonamido substituted diphenyl ureas as IL-8 receptor antagonists
INVENTOR(S): Widdowson, Katherine L.; Jin, Qi
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001068084	A1	20010920	WO 2001-US8672	20010316
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,				

YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
 BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1263427 A1 20021211 EP 2001-924195 20010316

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

JP 2003526664 T2 20030909 JP 2001-566648 20010316

BG 107013 A 20030530 BG 2002-107013 20020820

US 2003078250 A1 20030424 US 2002-220989 20020906

US 6664259 B2 20031216

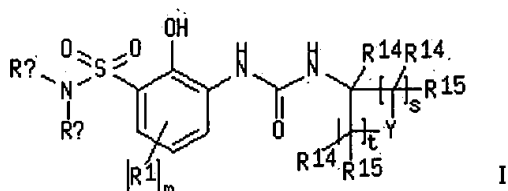
NO 2002004367 A 20021022 NO 2002-4367 20020912

PRIORITY APPLN. INFO.: US 2000-189848P P 20000316

WO 2001-US8672 W 20010316

OTHER SOURCE(S): MARPAT 135:257046

GI



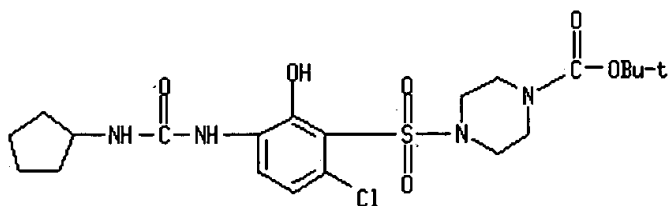
AB The title compds. [I; Rb = H, OH, aryl, etc.; m = 1-3; t = 0-2; s = 1-3; R1 = H, halo, NO2, etc.; Y = O, CO, NR14, etc.; R14, R15 = H, alkyl, ORa (Ra = alkyl, aryl, heteroaryl, etc.)] and their pharmaceutically acceptable salts, useful in the treatment of disease states mediated by the chemokine, Interleukin-8 (IL-8), were prepd. Thus, reacting 3-amino-6-chloro-2-hydroxybenzenesulfonamide (prepn. given) with cyclohexyl isocyanate in DMF afforded 52% I [Rb = H; R1 = 4-Cl; R14, R15 = H; t, s = 2; Y = CH2]. The IL-8, and GRO- α chemokine inhibitory effects of compds. I were detd. by in vitro assay (data given).

IT 361391-80-2P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses) (prepn. of sulfonamido substituted di-Ph ureas as IL-8 receptor antagonists)

RN 361391-80-2 HCAPLUS

CN 1-Piperazinecarboxylic acid, 4-[[6-chloro-3-[[[(cyclopentylamino)carbonyl]amino]-2-hydroxyphenyl]sulfonyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT:

5

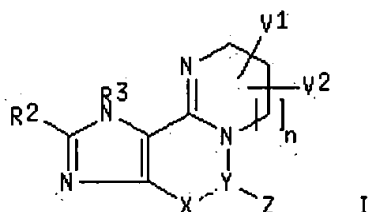
THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 18 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

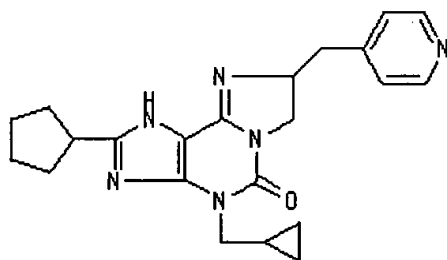
Full Text	Citing References
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ACCESSION NUMBER: 2001:489404 HCAPLUS
 DOCUMENT NUMBER: 135:76901
 TITLE: Preparation of quinazoline and quinoline derivatives
 as remedies for diseases mediated by
 autophosphorylation of PDGF receptors
 INVENTOR(S): Ueno, Kimihisa; Ogawa, Akira; Ohta, Yoshihisa; Nomoto,
 Yuji; Takasaki, Kotaro; Kusaka, Hideaki; Yano,
 Hiroshi; Suzuki, Chiharu; Nakanishi, Satoshi
 PATENT ASSIGNEE(S): Kyowa Hakko Kogyo Co., Ltd., Japan
 SOURCE: PCT Int. Appl., 126 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047931	A1	20010705	WO 2000-JP9160	20001222
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR PRIORITY APPLN. INFO.: JP 1999-366313 19991224 OTHER SOURCE(S): MARPAT 135:76901 GI				



I



II

AB Title compds. [I; X = N, CH; R3, R4, R5, R6 independently = H, Cl, F, CH3, CH3O, NO2; A = 4-CH3C6H4CH2OCONH, 3-ClC6H4CH(CH3)OCONH, 4-FC6H4CH2OCONH, 2-ClC6H4CH(CH3)OCONH, 2-ClC6H4CH2CH2CH2OCONH, 4-CF3C6H4CH2OCONH, CH3(CH2)5OCONH, (CH3CH2)2N(CH2)3NHCSNH, YNHCONH, 4-ClC6H4O(CH2)2S, 4-ClC6H4(CH2)2NH, 3-BrC6H4CONHCSNH, C6H5COO, OH, OCH2COOCH3, OCH2COOH; Y = heterocycle, heterocyclalkyl] and

pharmaceutically acceptable salts are prepd. as remedies for diseases mediated by autophosphorylation of PDGF receptors. Thus, the title claimed compd. II was prepd. and biol. tested.

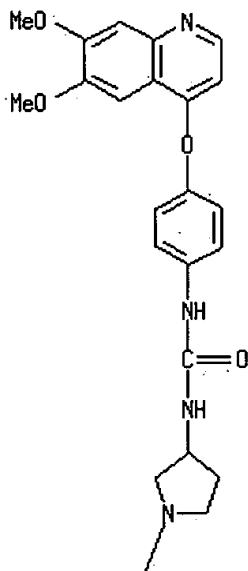
IT **347155-22-0P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of quinazolines and quinolines as remedies for diseases mediated by autophosphorylation of PDGF receptors)

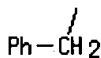
RN **347155-22-0** HCAPLUS

CN Urea, N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-[1-(phenylmethyl)-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

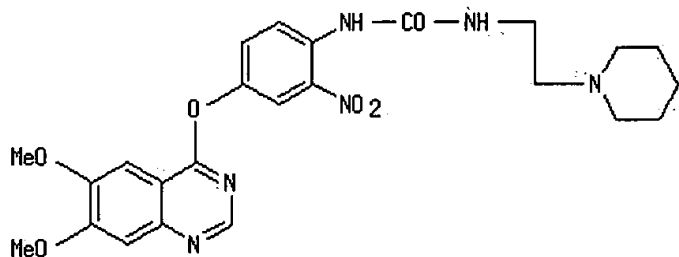
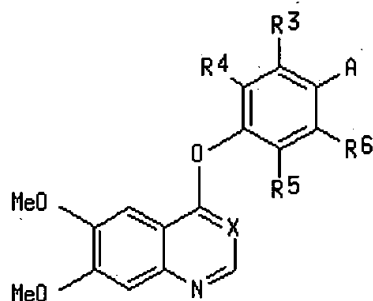
L24 ANSWER 19 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER:	2001:489372 HCAPLUS
DOCUMENT NUMBER:	135:92649
TITLE:	Preparation of quinazoline and quinoline derivatives as remedies for diseases mediated by autophosphorylation of PDGF receptors
INVENTOR(S):	Sakai, Teruyuki; Senga, Teruhumi; Furuta, Takayuki; Miwa, Atushi
PATENT ASSIGNEE(S):	Kirin Beer Kabushiki Kaisha, Japan
SOURCE:	PCT Int. Appl., 1068 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	Japanese
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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<u>WO 2001047890</u>	A1	20010705	<u>WO 2000-JP9157</u>	20001222
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
<u>AU 2001022232</u>	A5	20010709	<u>AU 2001-22232</u>	20001222
<u>EP 1243582</u>	A1	20020925	<u>EP 2000-985844</u>	20001222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
<u>PRIORITY APPLN. INFO.:</u>			<u>JP 1999-377486</u>	A 19991224
			<u>JP 1999-374494</u>	A 19991228
			<u>JP 2000-177790</u>	A 20000614
			<u>WO 2000-JP9157</u>	W 20001222
OTHER SOURCE(S):		MARPAT 135:92649		
GI				



AB Title compds. [I; X = N, CH; R3, R4, R5, R6 independently = H, Cl, F, CH3, CH3O, NO2; A = 4-CH3C6H4CH2OCONH, 3-ClC6H4CH(CH3)OCONH, 4-FC6H4CH2OCONH, 2-ClC6H4CH(CH3)OCONH, 2-ClC6H4CH2CH2CH2OCONH, 4-CF3C6H4CH2OCONH, CH3(CH2)5OCONH, (CH3CH2)2N(CH2)3NHCSNH, YNHCONH, 4-ClC6H4O(CH2)2S, 4-ClC6H4(CH2)2NH, 3-BrC6H4CONHCSNH, C6H5COO, OH, OCH2COOCH3, OCH2COOH; Y = heterocycle, heterocyclalkyl] and pharmaceutically acceptable salts are prepd. as remedies for diseases mediated by autophosphorylation of PDGF receptors, particularly useful as intimal thickening inhibitors. Thus, the title claimed compd. II was prepd. and biol. tested.

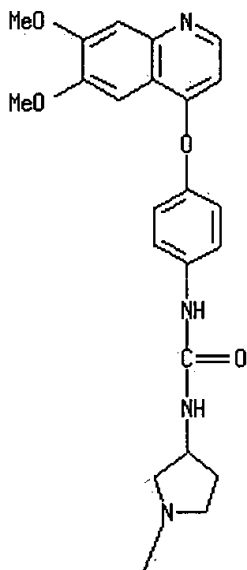
IT 347155-22-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of quinazolines and quinolines as remedies for diseases mediated by autophosphorylation of PDGF receptors)

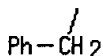
RN 347155-22-0 HCAPLUS

CN Urea, N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-[1-(phenylmethyl)-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 20 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2000:628110 HCAPLUS

DOCUMENT NUMBER: 133:222450

TITLE: Preparation of arylsulfonylaminoalkynoates as metalloprotease inhibitors

INVENTOR(S): Natchus, Michael George; Bookland, Roger Gunnard; Almstead, Neil Gregory; Pikul, Stanislaw; De, Biswanath; Cheng, Menyan

PATENT ASSIGNEE(S): Procter & Gamble Co., USA

SOURCE: PCT Int. Appl., 120 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

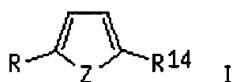
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2000051975	A1	20000908	WO 2000-US5162	20000301
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6197770	B1	20010306	US 2000-517080	20000301
NZ 513831	A	20010928	NZ 2000-513831	20000301
EP 1165501	A1	20020102	EP 2000-912064	20000301
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, IE, SI, LT, LV, FI, RO				
BR 2000008716	A	20020924	BR 2000-8716	20000301
JP 2002538136	T2	20021112	JP 2000-602203	20000301
AU 764051	B2	20030807	AU 2000-33860	20000301
AU 2000033860	A5	20000921		
ZA 2001006967	A	20020313	ZA 2001-6967	20010823
NO 2001004242	A	20010927	NO 2001-4242	20010831
PRIORITY APPLN. INFO.:			US 1999-122644P	P 19990303
			WO 2000-US5162	W 20000301
OTHER SOURCE(S):			MARPAT 133:222450	
GI				



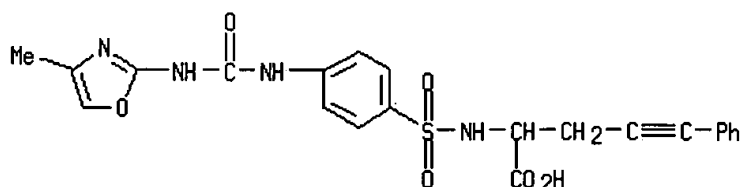
AB Title compds. [I; R = SO₂NR₂CR₁(COX)CR₃R₄(CR₅R₅')kZ₁R₁₃; R₁-R₅, R₅' = H or a substituent; R₁₃ = H, (un)substituted alkyl, -CONH₂, etc.; R₁₄ = cycloalkyl, heterocyclyl, DZ₂R₂₇, (un)substituted NH₂, etc.; D = O, S, CH:CH, N:N, etc.; R₂₇ = alkyl, (hetero)aryl, etc.; X = OH or NHOH; Z = O, S, CH:CH, (alkyl)imino, etc.; Z₁ = C≡C or (un)substituted CH:CH; Z₂ = bond or (un)substituted alkylene] were prepd. as metalloprotease inhibitors (no data). Thus, PhC≡CCH₂CH(NH₂)CO₂Me was N-acylated by 4-FC₆H₄C₆H₄(SO₂Cl)-4 to give, after sapon., PhC≡CCH₂(CO₂H)NHSO₂C₆H₄(C₆H₄F-4)-4.

IT 291533-73-8P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of arylsulfonylaminoalkynoates as metalloprotease inhibitors)

RN 291533-73-8 HCAPLUS

CN 4-Pentynoic acid, 2-[[[4-[[[(4-methyl-2-oxazolyl)amino]carbonyl]amino]phenyl]sulfonyl]amino]-5-phenyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS

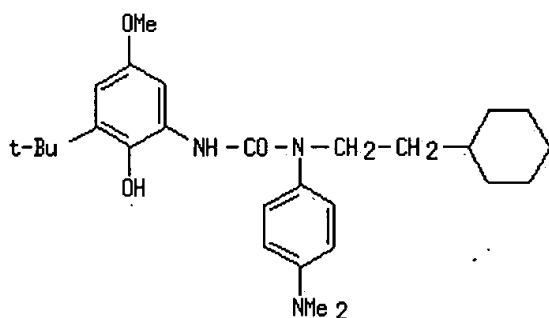
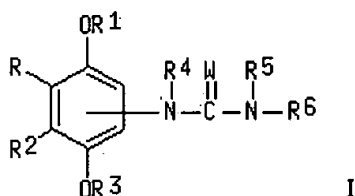
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 21 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 1999:332965 HCAPLUS
 DOCUMENT NUMBER: 131:44643
 TITLE: Preparation of phenol derivatives as antioxidants and ACAT inhibitors
 INVENTOR(S): Suzuki, Toshikazu; Ohmizu, Hiroshi; Hashimura, Yoshitada; Kubota, Hitoshi; Tanaka, Keiko
 PATENT ASSIGNEE(S): Tanabe Seiyaku Co., Ltd., Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 70 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 11139969	A2	19990525	JP 1998-220951	19980805
PRIORITY APPLN. INFO.:			JP 1997-212376	19970807
OTHER SOURCE(S):		MARPAT 131:44643		
GI				

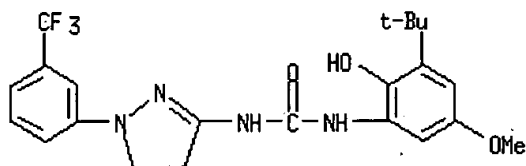


AB The title compds. I [R = H, (un)substituted alkyl, etc.; R1 = (un)substituted alkyl; R2 = (un)substituted alkyl, etc.; OR3= (protected) OH; R4 = H, (un)substituted alkyl, etc.; W = O, etc.; NR5R6 = (mono- or disubstituted) amino, etc.] are prepd. The title compd. II in vitro showed IC50 of 0.000067 μ M against ACAT.

IT **195312-41-5P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of phenol derivs. as antioxidants and ACAT inhibitors)

RN 195312-41-5 HCAPLUS
 CN Urea, N-[4,5-dihydro-1-[3-(trifluoromethyl)phenyl]-1H-pyrazol-3-yl]-N'-[3-(1,1-dimethylethyl)-2-hydroxy-5-methoxyphenyl]- (9CI) (CA INDEX NAME)



L24 ANSWER 22 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 1999:325902 HCAPLUS
 DOCUMENT NUMBER: 130:352546
 TITLE: Preparation of amides containing leucine or methionine for inhibition of the interaction of vascular cell-adhesion molecule-1 (VCAM-1) and fibronectin with integrin very late antigen 4 ($\alpha 4\beta 1$)
 INVENTOR(S): Brittain, David Robert; Johnstone, Craig
 PATENT ASSIGNEE(S): Zeneca Limited, UK
 SOURCE: PCT Int. Appl., 74 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9924398	A2	19990520	WO 1998-GB3334	19981109
WO 9924398	A3	19990805		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2308716	AA	19990520	CA 1998-2308716	19981109
AU 9910420	A1	19990531	AU 1999-10420	19981109
EP 1030835	A2	20000830	EP 1998-952872	19981109
EP 1030835	B1	20030122		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001522831	T2	20011120	JP 2000-520412	19981109
AT 231488	E	20030215	AT 1998-952872	19981109
ZA 9810330	A	19990512	ZA 1998-10330	19981111
NO 2000002158	A	20000711	NO 2000-2158	20000427
US 6344570	B1	20020205	US 2000-554224	20000711
PRIORITY APPLN. INFO.:			GB 1997-23789	A 19971112
			WO 1998-GB3334	W 19981109

OTHER SOURCE(S): MARPAT 130:352546
 GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I; R1 = II (in the para or meta position); R2, R3 = H, NO₂, alkyl, etc.; R2 and R3 together with the Ph to which they are attached form a 9-10 membered bicyclic ring system; R4 = alkyl; R5 = H, alkyl; R6 = alkyl, alkylcycloalkyl, alkylalkoxyl, etc.; R7 = alkyl, alkoxycarbonyl, alkenyl, etc.; R8 = (un)substituted aryl, heteroaryl, bicyclic heteroaryl ring system linked to the nitrogen via a ring carbon, etc.; R9, R10 = H, alkyl; NR8R9 = dihydroindolyl, dihydroquinolyl; R11 = CO₂H, tetrazolyl, alkyl sulfonylcarbonyl, sulfo, sulfinyl; Y = O, S, SO₂; m = 0-1; n = 0-4; with the proviso that when m and n cannot both be 0 and when m = 1, n = 0] and their pharmaceutically acceptable salts, useful in the treatment of multiple sclerosis, rheumatoid arthritis, asthma, coronary artery disease and psoriasis, were prepd. E.g., a multi-step synthesis of amide III was given. Compds. I are effective at 0.1-15 mg/kg/day.

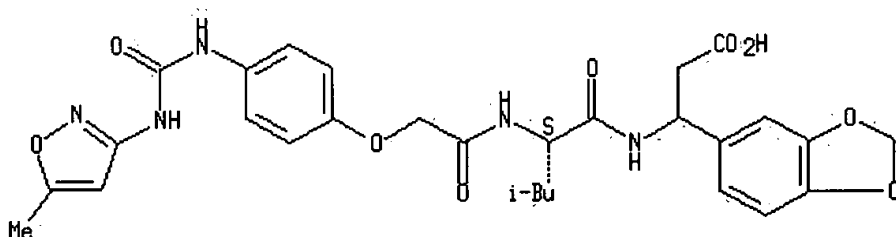
IT 225101-10-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of amides contg. leucine or methionine for inhibition of the interaction of vascular cell-adhesion mol.-1 (VCAM-1) and fibronectin with integrin very late antigen 4 ($\alpha 4\beta 1$))

RN 225101-10-0 HCAPLUS

CN β -Alanine, N-[[4-[[[(5-methyl-3-isoxazolyl)amino]carbonyl]amino]phenoxy]acetyl]-L-leucyl-3-(1,3-benzodioxol-5-yl)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L24 ANSWER 23 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 1999:311199 HCAPLUS

DOCUMENT NUMBER: 130:325145

TITLE: Preparation of aromatic heterocyclic compounds as antiinflammatory agents

INVENTOR(S): Regan, John R.; Cirillo, Pier F.; Hickey, Eugene R.; Moss, Neil; Cywin, Charles L.; Pargellis, Christopher; Gilmore, Thomas A.

PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 87 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9923091	A1	19990514	WO 1998-US22907	19981029

W: AU, BG, BR, BY, CA, CN, CZ, HR, HU, ID, IL, JP, KR, KZ, LT, LV,
MX, NO, NZ, PL, RO, RU, TR, UA, UZ, VN, YU
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE

CA 2308428	AA	19990514	CA 1998-2308428	19981029
AU 9913675	A1	19990524	AU 1999-13675	19981029
US 6080763	A	20000627	US 1998-181743	19981029
EP 1028953	A1	20000823	EP 1998-957405	19981029

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, FI

JP 2001521934	T2	20011113	JP 2000-518962	19981029
US 6228881	B1	20010508	US 1999-461446	19991214
US 2001039290	A1	20011108	US 2001-808084	20010314

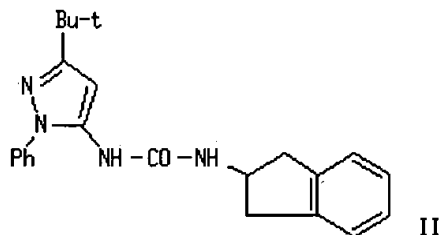
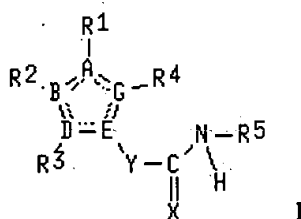
PRIORITY APPLN. INFO.:

US 1997-64102P	P	19971103
US 1998-181743	A3	19981029
WO 1998-US22907	W	19981029
US 1999-461446	A3	19991214

OTHER SOURCE(S) :

MARPAT 130:325145

GI



AB The title compds. I [A = C, N; B = C, N, O, etc.; D = C, N, S; E = C, N; G = C, S, N; X = S, O, etc.; Y = NH, etc.; R1 = (un)substituted, (partially or fully halogenated) alkyl, etc.; R2 is H, (partially or fully halogenated) alkyl, etc., when B is C or N; R3 is Ph, naphthyl, etc., when D is C or N; or R1R2 = fused Ph or pyridinyl ring; or R2R3 = fused Ph or pyridinyl ring; R4 is H, (partially or fully halogenated) alkyl when G is C or N; R5 is Ph, naphthyl, heteroaryl, etc.] are prepd. I inhibit prodn. of cytokines involved in immunoregulation and inflammation such as interleukin-1 and tumor necrosis factor. Pyrazole deriv. II was prepd. from phenylhydrazine and 4,4-dimethyl-3-oxopentanenitrile. Compds. of this invention had IC50 < 10 μ M against TNF prodn. in an in vitro assay using THP cells.

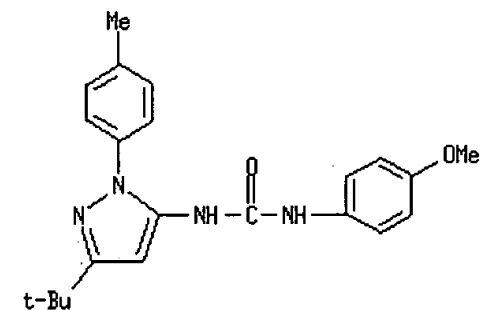
IT 223724-76-3P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of arom. heterocyclic compds. as antiinflammatory agents)

RN 223724-76-3 HCAPLUS

CN Urea, N-[3-(1,1-dimethylethyl)-1-(4-methylphenyl)-1H-pyrazol-5-yl]-N'-(4-

methoxyphenyl) - (9CI) (CA INDEX NAME)



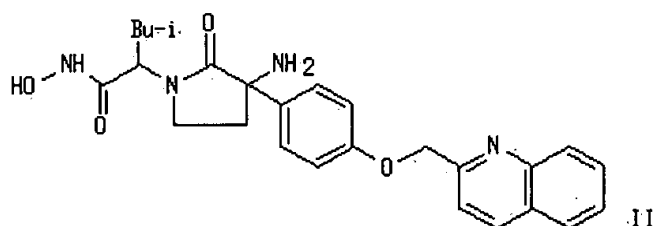
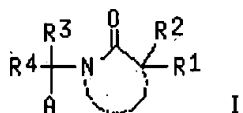
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 24 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 1999:244635 HCAPLUS
DOCUMENT NUMBER: 130:296611
TITLE: Preparation of novel lactam as metalloprotease inhibitors
INVENTOR(S): Duan, Jinguw; Decicco, Carl P.; Wasserman, Zelda R.; Maduskuie, Thomas P., Jr.
PATENT ASSIGNEE(S): Du Pont Pharmaceuticals Company, USA
SOURCE: PCT Int. Appl., 333 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9918074	A1	19990415	WO 1998-US21037	19981002
W: AU, BR, CA, CN, CZ, EE, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, UA, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
ZA 9808967	A	20000403	ZA 1998-8967	19981001
CA 2305679	AA	19990415	CA 1998-2305679	19981002
AU 9896866	A1	19990427	AU 1998-96866	19981002
AU 747239	B2	20020509		
US 6057336	A	20000502	US 1998-165747	19981002
EP 1027332	A1	20000816	EP 1998-950954	19981002
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
BR 9815398	A	20001031	BR 1998-15398	19981002
EE 200000199	A	20010416	EE 2000-200000199	19981002
JP 2001519331	T2	20011023	JP 2000-514886	19981002
NO 2000000783	A	20000529	NO 2000-783	20000217
PRIORITY APPLN. INFO.:			US 1997-62418P	P 19971003
			WO 1998-US21037	W 19981002
OTHER SOURCE(S):		MARPAT 130:296611		
GI				



AB Title compds. [I; A is selected from COOH, CH₂COOH, CONHOH, SH, CH₂SH, PO(OH)₂, etc.; ring B is a 4-8 membered cyclic amide contg. 0-3 heteroatoms from O, N, and S, etc.; R₁ is phenylmethoxyphenyl, phenoxyphenyl, etc.; R₂ is H, CH₃, Et, i-Pr, etc.; R₁-R₂ combine to form heterocyclic; R₃ is H, alkylene, heterocyclic, etc.; R₄ is H, alkylene, etc.; R₃-R₄ combine to form heterocyclic], stereoisomer, and pharmaceutically acceptable salt thereof are prepd. as useful metalloprotease inhibitors. Thus, compd. II was prepd. via alkylation, oxidn., amination, and cyclization.

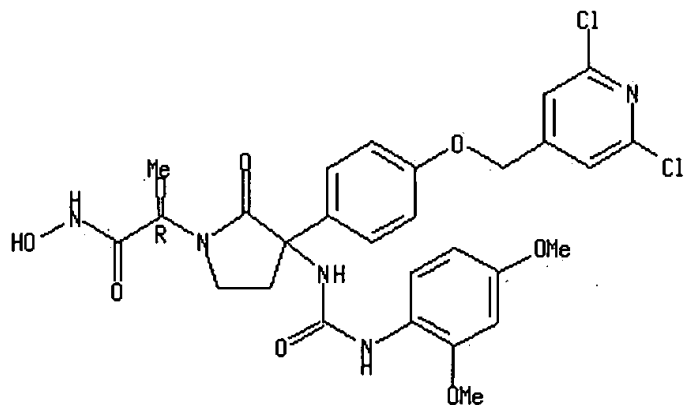
IT **223403-48-3P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of novel lactam metalloprotease inhibitors)

RN 223403-48-3 HCAPLUS

CN 1-Pyrrolidineacetamide, 3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-3-[[[(2,4-dimethoxyphenyl)amino]carbonyl]amino]-N-hydroxy-α-methyl-2-oxo-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

3

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

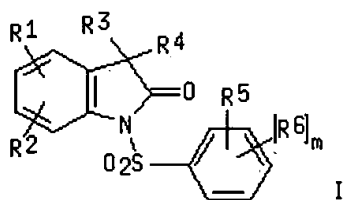
L24 ANSWER 25 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 1999:3288 HCAPLUS
 DOCUMENT NUMBER: 130:66390
 TITLE: Preparation of 1-benzenesulfonyl-1,3-dihydroindol-2-ones as vasopressin and/or oxytocin antagonists
 INVENTOR(S): Di Malta, Alain; Foulon, Loic; Garcia, Georges; Nisato, Dino; Roux, Richard; Serradeil-Legal, Claudine; Valette, Gerard; Wagnon, Jean
 PATENT ASSIGNEE(S): Sanofi, Fr.
 SOURCE: U.S., 53 pp., Cont.-in-part of U.S. Ser. No. 129,310, abandoned.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5849780	A	19981215	US 1994-323921	19941017
FR 2686878	A1	19930806	FR 1992-1034	19920130
FR 2686878	B1	19950630		
FR 2708605	A1	19950210	FR 1993-9404	19930730
EP 636608	A1	19950201	EP 1994-401737	19940728
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
US 5663431	A	19970902	US 1995-477571	19950607
US 5686624	A	19971111	US 1995-473302	19950607
US 5728723	A	19980317	US 1995-478738	19950607
US 5726322	A	19980310	US 1997-824305	19970326
PRIORITY APPLN. INFO.:			FR 1992-1034	A 19920130
			FR 1993-9404	A 19930730
			US 1993-129310	B2 19930930
			EP 1994-401737	A 19940728
			US 1994-323921	A3 19941017
			US 1995-473302	A3 19950607

OTHER SOURCE(S): MARPAT 130:66390
 GI



AB The title compds. [I; R1, R2 = H, OH, halo, etc.; R3R4 together with the carbon to which they are bonded = an optionally fused, (un)satd. (un)substituted C3-12 hydrocarbon ring; R5, R6 = H, halo, C1-7 alkyl, etc.; m = 1-4], having an affinity for the vasopressin V1 and V2 and/or oxytocin receptors, were prepd. Thus, treatment of 5-chloro-1,3-dihydro-3-spirocyclohexaneindol-2-one with NaH in THF followed by addn. of 2-methoxy-4-nitrobenzenesulfonyl chloride afforded I [R1 = 5-Cl; R2 = H; R3R4 = (CH₂)₅; R5 = 2-MeO; R6 = 4-NO₂]. Biol. data for compds. I are given.

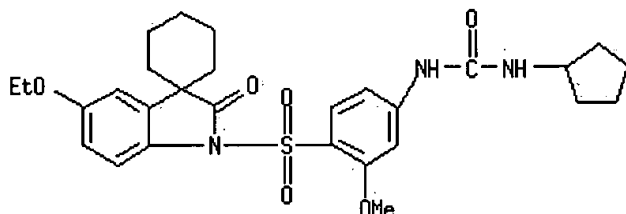
IT 161950-92-1P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use);

THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses) (prepn. of 1-benzenesulfonyl-1,3-dihydroindol-2-ones as vasopressin and/or oxytocin antagonists)

RN 161950-92-1 HCAPLUS

CN Spiro[cyclohexane-1,3'-[3H]indol]-2'-(1'H)-one, 1'-[[4-[(cyclopentylamino)carbonyl]amino]-2-methoxyphenyl]sulfonyl]-5'-ethoxy- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 26 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1998:42378 HCAPLUS
DOCUMENT NUMBER: 128:88682
TITLE: Preparation of hydroxyphenylureas as interleukin-8 receptor antagonists
INVENTOR(S): Widdowson, Katherine L.
PATENT ASSIGNEE(S): Smithkline Beecham Corp., USA; Widdowson, Katherine L.
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9749680	A1	19971231	WO 1997-US10903	19970624
W: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, GH, HU, IL, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9734091	A1	19980114	AU 1997-34091	19970624
EP 912505	A1	19990506	EP 1997-930204	19970624
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI				
BR 9709952	A	19990810	BR 1997-9952	19970624
JP 2000514049	T2	20001024	JP 1998-503448	19970624
ZA 9705743	A	19971229	ZA 1997-5743	19970627
TW 408102	B	20001011	TW 1997-86109211	19970912
NO 9806110	A	19990223	NO 1998-6110	19981223
KR 2000022274	A	20000425	KR 1998-710694	19981226
US 6133319	A	20001017	US 1999-202569	19990819

PRIORITY APPLN. INFO.:

US 1996-20658P P 19960627
US 1996-21973P P 19960627

WO 1997-US10903 W 19970624

OTHER SOURCE(S): MARPAT 128:88682

AB Title compds., e.g., RZNHC(:X)NHR1 [R = any functional moiety having an ionizable hydrogen and a pKa of ≤ 10 (sic); R1 = (un)substituted alk(en)yl or -alkynyl; Z = e.g., (un)substituted 1,2-phenylene] were prepd. Thus, 2-amino-5-nitrophenol was acylated by CH₂:CHCH₂NCO to give 2,4-(HO)(O₂N)C₆H₃NHCONHCH₂CH:CH₂. Data for biol. activity of title compds. were given.

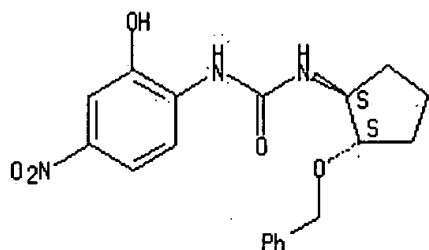
IT 201043-79-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of hydroxyphenylureas as interleukin-8 receptor antagonists)

RN 201043-79-0 HCAPLUS

CN Urea, N-(2-hydroxy-4-nitrophenyl)-N'-[2-(phenylmethoxy)cyclopentyl]-, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L24 ANSWER 27 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:589063 HCAPLUS

DOCUMENT NUMBER: 127:234183

TITLE: Ureidophenols as ACAT inhibitors and antioxidants

INVENTOR(S): Suzuki, Toshikazu; Ohmizu, Hiroshi; Hashimura, Yoshimasa; Kubota, Hitoshi; Tanaka, Keiko

PATENT ASSIGNEE(S): Tanabe Seiyaku Co., Ltd., Japan

SOURCE: Eur. Pat. Appl., 84 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

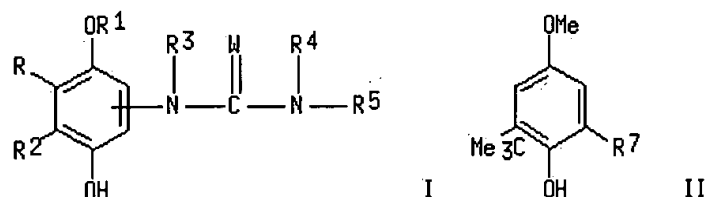
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 790240	A1	19970820	EP 1997-102315	19970213
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CA 2197364	AA	19970816	CA 1997-2197364	19970212
JP 10195037	A2	19980728	JP 1997-28582	19970213
US 5849732	A	19981215	US 1997-800680	19970214
CN 1165815	A	19971126	CN 1997-101973	19970217
PRIORITY APPLN. INFO.:			JP 1996-28083	19960215
			JP 1996-300032	19961112

OTHER SOURCE(S): MARPAT 127:234183

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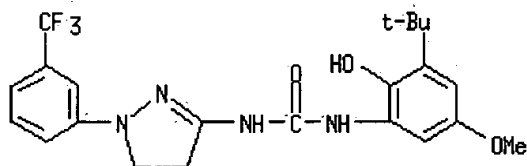
AB Ureidophenols I [R = H, alkyl, alkyloxy; R1 = alkyl; R2 = alkyl, alkoxy; R3 = H, alkyl, acyl; W = O, S or NR6; NR4R5 = (un)substituted NH2, N heterocycle; R6 = H, alkyl, aryl, OH, alkoxy] were prepd. I possess both an ACAT inhibitory activity and an antioxidative activity (no data). Thus, 4,2-MeO(Me3C)C6H3OH was treated with 4-MeOC6H4NH2 to give the azobenzene II [R7 = N:NC6H4OMe-4], which was O-protected, reduced to the amine, treated with PhNCO, and O-deprotected to give the ureidophenol II [R7 = NHCONHPh].

IT 195312-41-5P

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (prepn. of ureidophenols as ACAT inhibitors and antioxidants)

RN 195312-41-5 HCAPLUS

CN Urea, N-[4,5-dihydro-1-[3-(trifluoromethyl)phenyl]-1H-pyrazol-3-yl]-N'-[3-(1,1-dimethylethyl)-2-hydroxy-5-methoxyphenyl]- (9CI) (CA INDEX NAME)



L24 ANSWER 28 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER:

1996:241537 HCAPLUS

DOCUMENT NUMBER:

124:289561

TITLE:

Preparation of thienopyrimidinones as cyclic GMP phosphodiesterase inhibitors

INVENTOR(S):

Oota, Tomoki; Kawashima, Yutaka; Hatayama, Katsuo

PATENT ASSIGNEE(S):

Taisho Pharma Co Ltd, Japan

SOURCE:

Jpn. Kokai Tokkyo Koho, 20 pp.

CODEN: JKXXAF

DOCUMENT TYPE:

Patent

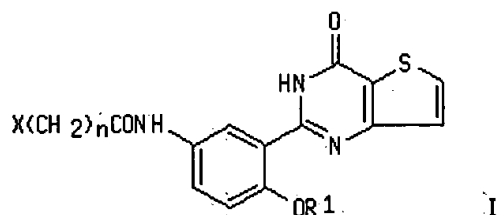
LANGUAGE:

Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 07330777	A2	19951219	JP 1994-126555	19940608
PRIORITY APPLN. INFO.:			JP 1994-126555	19940608
OTHER SOURCE(S):			MARPAT 124:289561	
GI				



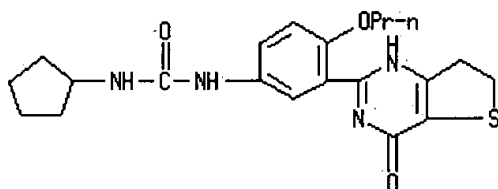
AB The title compds. I [R1 = alkyl; n = 0 or 1; X = halo, cycloalkyl, etc.] are prepd. I [X = morpholino; n = 0; R1 = ethyl] (prepn. given) at 28 µg/Kg decreased blood pressure in rats by 15 mmHg.

IT **175595-13-8P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses) (prepn. of thienopyrimidinones as cyclic GMP phosphodiesterase inhibitors)

RN **175595-13-8** HCAPLUS

CN Urea, N-cyclopentyl-N'-[4-propoxy-3-(1,4,6,7-tetrahydro-4-oxothieno[3,2-d]pyrimidin-2-yl)phenyl]- (9CI) (CA INDEX NAME)



L24 ANSWER 29 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:890151 HCAPLUS

DOCUMENT NUMBER: 123:285554

TITLE: Preparation of arylureas as cholesterol acyltransferase inhibitors

INVENTOR(S): Sueda, Noriyoshi; Yamada, Kazuhiko; Yanai, Makoto; Miura, Katsutoshi; Horigome, Masato; Oshida, Norio; Hiramoto, Shigeru; Katsuyama, Koichi; Nakata, Fumihisa; et al.

PATENT ASSIGNEE(S): Nisshin Flour Milling Co., Ltd., Japan

SOURCE: Eur. Pat. Appl., 49 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

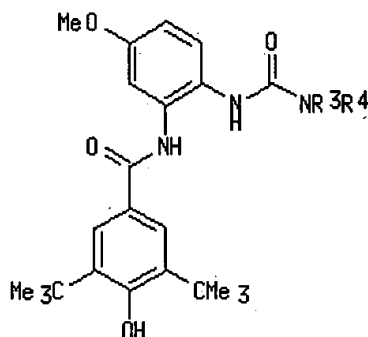
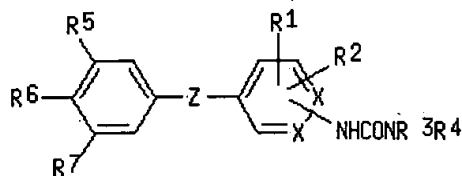
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 665216	A1	19950802	EP 1994-307398	19941010
EP 665216	B1	19971229		
R: DE, FR, GB, IT				
US 5576335	A	19961119	US 1994-314814	19940929
CA 2133394	AA	19950802	CA 1994-2133394	19940930
JP 07258199	A2	19951009	JP 1994-270205	19941011
PRIORITY APPLN. INFO.:			JP 1994-27560	19940201

OTHER SOURCE(S): MARPAT 123:285554

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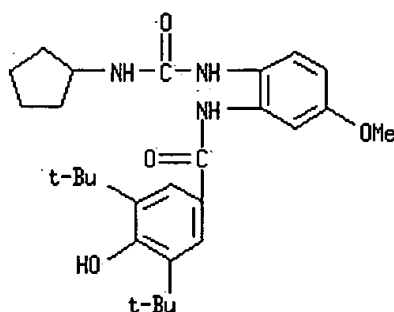
AB Title compds. [I; R1,R2 = H, halo, alkoxy; R3,R4 = H, (ar)alkyl, etc.; NR3R4 = heterocyclyl; R5,R7 = H, alkyl; R6 = OR8, N(R8)2; R6R7 = OCH2O, etc.; R8 = H, alkyl, CONHR3; X = N, CH; Z = CONR9, O2C, O(CH2)3, etc.; R9 = H, alkyl, alkanoyl, etc.] were prepd. Thus, 4-methoxy-2-nitroaniline was acylated by ClCO2Ph and the product amidated by cyclopentylamine to give, after hydrogenation and amidation by 3,5-di-tert-butyl-4-hydroxybenzoic acid, title compd. II (R3 = H, R4 = cyclopentyl). II (R3 = R4 = CH2Ph) gave 99% inhibition of cholesterol acyltransferase at 10⁻⁷M in vitro.

IT 169604-08-4P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of arylureas as cholesterol acyltransferase inhibitors)

RN 169604-08-4 HCAPLUS

CN Benzamide, N-[2-[[[(cyclopentylamino)carbonyl]amino]-5-methoxyphenyl]-3,5-bis(1,1-dimethylethyl)-4-hydroxy- (9CI) (CA INDEX NAME)



L24 ANSWER 30 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 1995:464454 HCAPLUS

DOCUMENT NUMBER: 122:213926

TITLE: 1-Benzenesulfonyl-1,3-dihydro-indol-2-one derivatives,

their preparation, and pharmaceutical compositions containing them.

INVENTOR(S): Di, Malta Alain; Foulon, Loic; Garcia, Georges; Nisato, Dino; Roux, Richard; Serradeil-Legal, Claudine; Valette, Gerard; Wagnon, Jean

PATENT ASSIGNEE(S): Sanofi, Fr.

SOURCE: Eur. Pat. Appl., 55 pp.
CODEN: EPXXDW

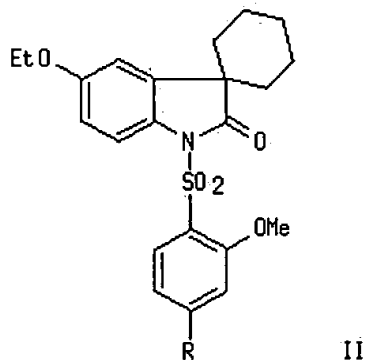
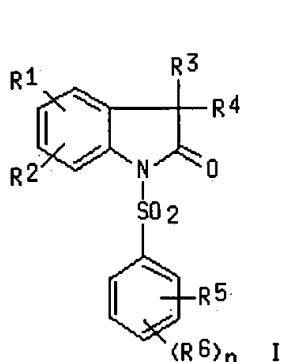
DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 636608	A1	19950201	EP 1994-401737	19940728
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
FR 2708605	A1	19950210	FR 1993-9404	19930730
IL 110482	A1	19990411	IL 1994-110482	19940728
CA 2129215	AA	19950131	CA 1994-2129215	19940729
FI 9403570	A	19950131	FI 1994-3570	19940729
NO 9402834	A	19950131	NO 1994-2834	19940729
AU 9468789	A1	19950209	AU 1994-68789	19940729
AU 684791	B2	19980108		
ZA 9405656	A	19950309	ZA 1994-5656	19940729
HU 70408	A2	19951030	HU 1994-2232	19940729
RU 2141476	C1	19991120	RU 1994-27576	19940729
CN 1107467	A	19950830	CN 1994-114900	19940730
JP 07247269	A2	19950926	JP 1994-199069	19940801
US 5849780	A	19981215	US 1994-323921	19941017
US 5686624	A	19971111	US 1995-473302	19950607
US 5726322	A	19980310	US 1997-824305	19970326
<u>PRIORITY APPLN. INFO.:</u>			FR 1993-9404	A 19930730
			FR 1992-1034	A 19920130
			US 1993-129310	B2 19930930
			EP 1994-401737	A 19940728
			US 1994-323921	A3 19941017
			US 1995-473302	A3 19950607
OTHER SOURCE(S):		CASREACT 122:213926; MARPAT 122:213926		
GI				



AB Title compds. I [R1, R2 = H, OH, halo, haloalkoxy, alkyl, CF3, alkoxy, etc.; R3, R4 = alkyl, cycloalkyl, Ph, PhCH2, hydroxyalkyl, etc.; or R3R4 = (CH2)pX(CH2)q; or R3R4 forms an (un)substituted (un)satd. hydrocarbon ring; R5, R6 = H, halo, alkyl, CF3, cyano, OH, NO2, (un)substituted NH2,

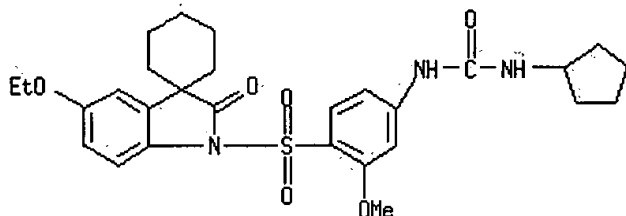
CO₂H, etc.; X = O, SO_n, NH or derivs.; m = 1, or (when R₆ = halo, alkyl, or alkoxy) also 2-4, or (for multiple but different R₆) also > 1; n = 0-2; (p + q) = 3-6; numerous addnl. definitions and provisos] and their salts are claimed. Over 80 synthetic examples are given. Thus, 5-ethoxy-1,3-dihydro-3-spirocyclohexaneindol-2-one [prepn. given] was treated with NaH in THF and then N-sulfonylated with 2-methoxy-4-nitrobenzenesulfonyl chloride. Redn. of the nitro group in the product with Fe and HCl and cyclization of the resultant amine with cis-1,4-dichloro-2-butene gave a mixt. of title compds. II [R = 1-pyrrolidinyl and 1-(3-pyrrolinyl)], which were hydrogenated over Pd/C to give II (R = 1-pyrrolidinyl). In various assays, I bound to V1 and V2 vasopressin receptors with IC₅₀ values down to 10⁻⁷ and 10⁻⁹ M, resp., and bound to oxytocin receptors with IC₅₀ down to 10⁻⁸ M. The compds. also showed oral activity (no data).

IT **161950-92-1P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of benzenesulfonyldihydroindolone derivs. as vasopressin and/or oxytocin antagonists)

RN **161950-92-1** HCAPLUS

CN Spiro[cyclohexane-1,3'-[3H]indol]-2'-(1'H)-one, 1'-[[4-
[[[(cyclopentylamino)carbonyl]amino]-2-methoxyphenyl]sulfonyl]-5'-ethoxy-
(9CI) (CA INDEX NAME)



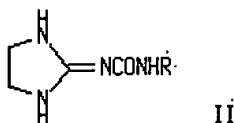
L24 ANSWER 31 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 1982:68993 HCAPLUS
DOCUMENT NUMBER: 96:68993
TITLE: N-(Substituted phenyl)-N'-(2-imidazolidinylidene)ureas
INVENTOR(S): Rasmussen, Chris R.
PATENT ASSIGNEE(S): McNeil Laboratories, Inc., USA
SOURCE: U.S., 7 pp. Cont.-in-part of U.S. 4,229,462.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4298746	A	19811103	US 1980-156900	19800606
US 4229462	A	19801021	US 1978-972579	19781222
ZA 7906965	A	19810729	ZA 1979-6965	19791221
GB 2113204	A1	19830803	GB 1982-21517	19820726
GB 2113204	B2	19840201		
PRIORITY APPLN. INFO.:			US 1978-972579	19781222
			US 1978-972580	19781222
			GB 1979-44114	19791221

OTHER SOURCE(S) : CASREACT 96:68993
GI



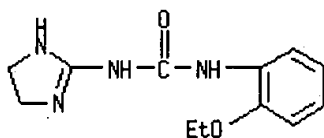
AB The reaction of 2-iminoimidazolidine (I) with RNCO (R = methyl-, chloro-, bromo-, or methoxyphenyl) yielded the resp. ureas II, which exhibited antihypertensive activity. I, 2,6-Cl₂C₆H₃NCO, and Na₂SO₄ in THF-DMF was stirred overnight to give II (R = 2,6-Cl₂C₆H₃).

IT **80625-17-8**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antihypertensive activity of)

RN **80625-17-8** HCAPLUS

CN Urea, N-(4,5-dihydro-1H-imidazol-2-yl)-N'-(2-ethoxyphenyl)- (9CI) (CA INDEX NAME)



L24 ANSWER 32 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 1981:132015 HCAPLUS

DOCUMENT NUMBER: 94:132015

TITLE: Interrelationship between anticonvulsant and enzyme inhibitor properties of N-methyl-N-[2-(1-arylthiocarbamido)cyclopentyl]nitrobenzamides

AUTHOR(S): Pandey, Ghagwan R.; Singh, Shiva P.; Brumleve, Stanley J.; Parmar, Surendra S.

CORPORATE SOURCE: Dep. Pharmacol. Therapeutics, Lucknow Univ., Lucknow, 226003, India

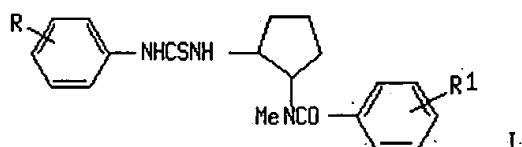
SOURCE: Pharmacological Research Communications (1981), 13(1), 65-74

CODEN: PLRCAT; ISSN: 0031-6989

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



AB A series of N-methyl-N-[2-(1-arylthiocarbamido)cyclopentyl]nitrobenzamides I (R = H, 2-Me, 2-OMe etc; R' = 2- or 4-NO₂) were synthesized and

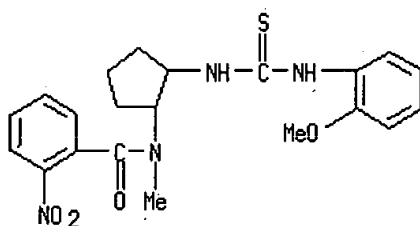
evaluated for their anticonvulsant activity and potentiation of pentobarbital-induced hypnosis. These compds. were also investigated for their ability to inhibit pyruvate oxidase [9001-96-1] and monoamine oxidase [9001-66-5]. No structural correlation between the central nervous system depressant and the enzyme inhibitory properties of these I was apparent.

IT 77051-85-5P

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(prepn. and pharmacol. of, structure in relation to)

RN 77051-85-5 HCAPLUS

CN Benzamide, N-[2-[[[(2-methoxyphenyl)amino]thioxomethyl]amino]cyclopentyl]-N-methyl-2-nitro- (9CI) (CA INDEX NAME)



L24 ANSWER 33 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 1971:141216 HCAPLUS

DOCUMENT NUMBER: 74:141216

TITLE: Chemotherapeutic agents against Mycobacterium tuberculosis. XXVI. Synthesis and antituberculous activity of phenylthiourea, p-ethoxyphenylthiourea, and 3-bromo-4-ethoxyphenylthiourea derivatives

AUTHOR(S): Fujikawa, Fukujiro; Hirai, Kunio; Hirayama, Teruhisa; Matsunashi, Teruki; Nakanishi, Yoshikuni; Kumoto, Kayoko; Shimizu, Tatsuzo; Sakaki, Chiichiro; Hamuro, Yoshitaro; et al.

CORPORATE SOURCE: Kyoto Coll. Pharm., Kyoto, Japan

SOURCE: Yakugaku Zasshi (1971), 91(2), 159-65

CODEN: YKKZAJ; ISSN: 0031-6903

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

GI For diagram(s), see printed CA Issue.

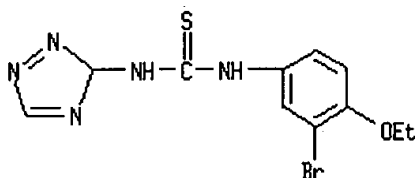
AB Seventy-five thioureas, comprising 27 derivs. of phenylthiourea (I), 25 of p-ethoxyphenylthiourea (II), and 23 of 3-bromo-4-ethoxyphenylthiourea (III), were prepd. from corresponding phenyl isothiocyanates and tested for antibacterial activity against a strain of human-type, drug-sensitive Mycobacterium tuberculosis in vitro. Six of them were active, but their min. inhibitory concns. (MIC) were significantly higher than those of control agents, such as isoniazid and p-aminosalicylic acid. The MIC of 1-phenyl-3-[4-(dimethylamino)-phenyl]-2-thiourea and 1-(4-ethoxyphenyl)-3-(4-bromophenyl)-2-thiourea were 3.13 and 6.25 °mg/ml, resp.

IT 31864-67-2

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antitubercular activity of)

RN 31864-67-2 HCAPLUS

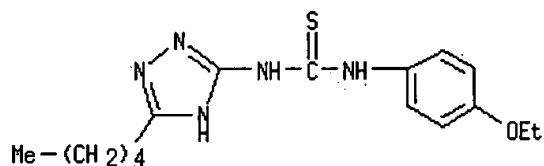
CN Urea, 1-(3-bromo-4-ethoxyphenyl)-2-thio-3-s-triazol-3-yl- (8CI) (CA INDEX NAME)



L24 ANSWER 34 OF 34 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 1969:103962 HCAPLUS
DOCUMENT NUMBER: 70:103962
TITLE: Synthesis and study of thiocarbamide derivatives. IV. Correlation between structure and tuberculostatic activity of 1H-1,2,4-triazole, 1,3-indandione, and 4-methoxybenzaldehyde thiourea derivatives
AUTHOR(S): Grinsteins, V.; Medne, K.; Sausins, A.; Cipens, G.; Bokalders, R.
CORPORATE SOURCE: Inst. Org. Sin., Riga, USSR
SOURCE: Latvijas PSR Zinatnu Akademijas Vestis, Kimijas Serija (1968), (6), 691-8
CODEN: LZAKAM; ISSN: 0002-3248
DOCUMENT TYPE: Journal
LANGUAGE: Russian
GI For diagram(s), see printed CA Issue.
AB The tuberculostatic activity of some thioureas was detd. in vitro, using the drug-sensitive Mycobacterium tuberculosis strains H37Rv and Ravenel and also the resistant strains Vallee and D. The following I were tested (R and R' given): Ph, H; Me, H; H, OEt (II); Me, OEt (III); Pr, OEt (IV); Me(CH₂)₄, OEt (V); Me, OPr (VI); Me, O(CH₂)₄Me (VII). VIII and 5-thiocarbamoyl-1H-1,2,4-triazole were similarly tested. Only IIVII had high antitubercular activity. The following IX were also tested (R and R' given): H, H; H, OMe; H, o-OMe; H, OEt (X); H, Me; H, Br; H, I; OMe, H; OMe, OMe; OMe, o-OMe; OMe, OEt; OMe, Me; OMe, I; OMe, Br. IX had low antitubercular activity, except X. The following XI were also tested (R given): Ph; p-MeC₆H₄ (XII); p-EtOC₆H₄; p-Pr-OC₆H₄; p-iso-PrOC₆H₄; p-BuOC₆H₄; p-iso-BuOC₆H₄; p-Me-(CH₂)₄OC₆H₄; p-BrC₆H₄; p-IC₆H₄; 2-C₁₀H₇. Also tested was the ortho analog (XIII) of XII. XII and XIII had some activity. XIV (R = MeO, Br, or I) were practically inactive. p-[2,5-MeO(HCO)C₆H₃NHCSNH]C₆H₄R (R = H, MeO, o-EtO, PrO, BuO, Me(CH₂)₄O, or Br) and 4,3-MeO(p-BuOC₆H₄NHCSNH)-C₆H₃CH:NNHC(NH₂):NH.HCl were studied. In this class also, alkoxy-contg. compds. were most active. Addn. of blood serum to the nutrient medium of the microorganisms reduced the activity of the most effective compds. to 1/30-1/2.
IT 21731-95-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tuberculostatic activity of)
RN 21731-95-3 HCAPLUS
CN Urea, 1-(p-ethoxyphenyl)-3-(5-pentyl-s-triazol-3-yl)-2-thio- (8CI) (CA INDEX NAME)



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(FILE 'HOME' ENTERED AT 21:09:03 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 21:09:18 ON 29 MAR 2004

L1 STRUCTURE UPLOADED
L2 2 S L1
L3 787 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 21:10:37 ON 29 MAR 2004

L4 46 S L3/THU
L5 5 S L4 AND DUMAS, J?/AU
L6 41 S L4 NOT L5
L7 0 S L6 AND KHIRE, U?/AU
L8 1 S L6 AND LOWINGER, T?/AU
L9 1 S L6 AND PAULSEN, H?/AU
L10 40 S L6 NOT L8
L11 1 S L10 AND PAULSEN, H?/AU
L12 39 S L10 NOT L11
L13 0 S L12 AND RIEDL, B?/AU
L14 0 S L12 AND SCOTT, W?/AU
L15 0 S L12 AND SMITH, R?/AU
L16 0 S L12 AND WOOD, W?/AU
L17 0 S L12 AND HATOUM-MOKDAD, H?/AU
L18 0 S L12 AND JOHNSON, J?/AU
L19 0 S L12 AND LEE, W?/AU
L20 0 S L12 AND REDMAN, A?/AU
L21 0 S L12 AND SIBLEY, R?/AU
L22 0 S L12 AND RENICK, J?/AU
L23 5 S L12 AND CANC?
L24 34 S L12 NOT L23
L25 0 S L24, IBIB ABS FHITSTR, 1-34

=> s 13

L26 151 L3

=> file caold

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	244.75	400.80
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-31.88	-31.88

FILE 'CAOLD' ENTERED AT 21:16:57 ON 29 MAR 2004

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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FILE COVERS 1907-1966

FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REGISTRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

=> d his

(FILE 'HOME' ENTERED AT 21:09:03 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 21:09:18 ON 29 MAR 2004

L1 STRUCTURE UPLOADED
L2 2 S L1
L3 787 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 21:10:37 ON 29 MAR 2004

L4 46 S L3/THU
L5 5 S L4 AND DUMAS, J?/AU
L6 41 S L4 NOT L5
L7 0 S L6 AND KHIRE, U?/AU
L8 1 S L6 AND LOWINGER, T?/AU
L9 1 S L6 AND PAULSEN, H?/AU
L10 40 S L6 NOT L8
L11 1 S L10 AND PAULSEN, H?/AU
L12 39 S L10 NOT L11
L13 0 S L12 AND RIEDL, B?/AU
L14 0 S L12 AND SCOTT, W?/AU
L15 0 S L12 AND SMITH, R?/AU
L16 0 S L12 AND WOOD, W?/AU
L17 0 S L12 AND HATOUM-MOKDAD, H?/AU
L18 0 S L12 AND JOHNSON, J?/AU
L19 0 S L12 AND LEE, W?/AU
L20 0 S L12 AND REDMAN, A?/AU
L21 0 S L12 AND SIBLEY, R?/AU
L22 0 S L12 AND RENICK, J?/AU
L23 5 S L12 AND CANC?
L24 34 S L12 NOT L23
L25 0 S L24, IBIB ABS FHITSTR, 1-34
L26 151 S L3

FILE 'CAOLD' ENTERED AT 21:16:57 ON 29 MAR 2004

=> s l3

L27 14 L3

=> s l3 and can?

14 L3
17544 CAN?
L28 0 L3 AND CAN?

=> d l27, all, 1-14

L27 ANSWER 1 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

Full
Text

AN CA65:720g CAOLD
 TI 5-methyloxazoline, urea derivs. of
 PA Chemische Werke Albert
 DT Patent
 TI urea derivs. of 5-methyloxazoline
 AU Zimmermann, Rolf; Koch, K.; Englisch, A.
 DT Patent

PATENT NO.	KIND	DATE
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PI GB 1023386IT 1750-38-5 1750-39-6 1963-13-9 2318-76-5 6449-68-9 31788-64-4

L27 ANSWER 2 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

Full
Text

AN CA65:204b CAOLD
 TI color couplers
 AU Franchi, Luigi; Magagnoli, R.
 DT Patent

PATENT NO.	KIND	DATE
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PI FR 1403481IT 2489-28-3 10555-22-3 10555-23-4 13014-99-8 30424-07-8

L27 ANSWER 3 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

Full
Text

AN CA64:16037g CAOLD
 TI 1-fluoroalkyl-2-pyrazolin-5-one color couplers
 PA Gevaert-Agfa N. V.
 DT Patent

PATENT NO.	KIND	DATE
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PI NL 6509593BE 667370FR 1441166

IT	<u>1439-40-3</u>	<u>1439-63-0</u>	<u>1439-64-1</u>	<u>1908-58-3</u>	<u>5355-07-7</u>	<u>5355-08-8</u>
	<u>5376-72-7</u>	<u>5376-74-9</u>	<u>5376-75-0</u>	<u>5376-76-1</u>	<u>5376-77-2</u>	<u>5376-78-3</u>
	<u>5376-79-4</u>	<u>5376-80-7</u>	<u>5377-19-5</u>	<u>5528-93-8</u>	<u>5529-15-7</u>	<u>5529-17-9</u>
	<u>5529-18-0</u>	<u>5529-19-1</u>	<u>5529-20-4</u>	<u>5529-21-5</u>	<u>5529-22-6</u>	<u>5529-23-7</u>
	<u>5529-24-8</u>	<u>5529-25-9</u>	<u>5529-26-0</u>	<u>5529-27-1</u>	<u>6887-07-6</u>	<u>96764-55-5</u>

L27 ANSWER 4 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

Full
Text

AN CA64:9862b CAOLD
 TI mercaptan-forming couplers
 AU Barr, Charles R.; Williams, J.; Whitmore, K. E.
 PA Eastman Kodak Co.
 DT Patent

PATENT NO.	KIND	DATE
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PI US 3227554

1966

IT	<u>5083-12-5</u>	<u>5083-13-6</u>	<u>5083-14-7</u>	<u>5083-15-8</u>	<u>5083-16-9</u>	<u>5083-17-0</u>
	<u>5083-18-1</u>	<u>5083-19-2</u>	<u>5083-20-5</u>	<u>5083-21-6</u>	<u>5083-22-7</u>	<u>5083-23-8</u>
	<u>5083-24-9</u>	<u>5104-70-1</u>	<u>5104-71-2</u>	<u>5104-72-3</u>	<u>5104-73-4</u>	<u>5104-74-5</u>
	<u>5104-75-6</u>	<u>5104-76-7</u>	<u>5104-77-8</u>	<u>5104-78-9</u>	<u>5104-79-0</u>	<u>5104-80-3</u>
	<u>5104-81-4</u>	<u>5104-82-5</u>	<u>5104-83-6</u>	<u>5181-56-6</u>	<u>5181-57-7</u>	<u>5181-58-8</u>

<u>5181-59-9</u>	<u>5181-60-2</u>	<u>5181-61-3</u>	<u>5489-27-0</u>	<u>5489-28-1</u>	<u>5489-29-2</u>
<u>5489-30-5</u>	<u>5489-31-6</u>	<u>5489-32-7</u>	<u>5489-33-8</u>	<u>5489-34-9</u>	<u>5489-35-0</u>
<u>5489-36-1</u>	<u>5489-37-2</u>	<u>5489-38-3</u>	<u>5489-39-4</u>	<u>5489-40-7</u>	<u>5489-41-8</u>
<u>5489-42-9</u>	<u>5489-43-0</u>	<u>5489-44-1</u>	<u>5489-45-2</u>	<u>5489-46-3</u>	<u>5489-47-4</u>
<u>5489-48-5</u>	<u>5489-49-6</u>	<u>5546-04-3</u>	<u>5546-05-4</u>	<u>5546-06-5</u>	<u>5546-81-6</u>
<u>5563-00-8</u>	<u>5563-01-9</u>	<u>5577-21-9</u>	<u>5577-22-0</u>	<u>5577-23-1</u>	<u>5577-24-2</u>
<u>5577-25-3</u>	<u>5610-81-1</u>	<u>5611-25-6</u>	<u>5996-74-7</u>	<u>6016-46-2</u>	<u>6016-47-3</u>
<u>6016-48-4</u>	<u>6016-49-5</u>	<u>6016-50-8</u>	<u>6016-51-9</u>	<u>6019-55-2</u>	<u>6019-56-3</u>
<u>6019-57-4</u>	<u>6019-67-6</u>	<u>6019-68-7</u>	<u>6056-79-7</u>	<u>6168-15-6</u>	<u>6190-09-6</u>
<u>6400-04-0</u>	<u>6667-82-9</u>	<u>6823-60-5</u>	<u>6892-16-6</u>	<u>30898-81-8</u>	<u>30998-55-1</u>
<u>90350-82-6</u>	<u>96765-70-7</u>	<u>97828-89-2</u>	<u>97924-93-1</u>	<u>98945-77-8</u>	<u>105976-61-2</u>
<u>106438-97-5</u>	<u>106439-05-8</u>	<u>108015-55-0</u>	<u>108015-56-1</u>		

L27 ANSWER 5 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

AN CA64:5237c CAOLD

TI magenta photographic couplers

AU Bellone, Domenico; Chittolini, U.; Guzzi, A.

DT Patent

IT	<u>614-16-4</u>	<u>1779-08-4</u>	<u>1788-10-9</u>	<u>2412-05-7</u>	<u>4581-46-8</u>	<u>4622-67-7</u>
	<u>4640-64-6</u>	<u>4644-43-3</u>	<u>4644-44-4</u>	<u>4644-45-5</u>	<u>4644-46-6</u>	<u>4644-47-7</u>
	<u>4644-48-8</u>	<u>4644-49-9</u>	<u>4644-50-2</u>	<u>4644-51-3</u>	<u>4644-52-4</u>	<u>4644-53-5</u>
	<u>4644-54-6</u>	<u>4644-55-7</u>	<u>4644-56-8</u>	<u>4644-57-9</u>	<u>4644-58-0</u>	<u>4644-59-1</u>
	<u>4681-06-5</u>	<u>4692-10-8</u>	<u>4772-97-8</u>	<u>4779-36-6</u>	<u>4779-37-7</u>	

L27 ANSWER 6 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

Full
Text

AN CA64:3550f CAOLD

TI cyclohept[d]imidazoles

AU Sunagawa, Genshun; Nakao, H.

PA Sankyo Co., Ltd.

DT Patent

PATENT NO.	KIND	DATE
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PI JP 65020707

1965

IT	<u>2048-43-3</u>	<u>2048-44-4</u>	<u>2048-45-5</u>	<u>2048-46-6</u>	<u>2048-47-7</u>	<u>2048-48-8</u>
	<u>2048-49-9</u>	<u>2132-29-8</u>	<u>2132-30-1</u>	<u>2409-67-8</u>	<u>2535-45-7</u>	<u>2536-06-3</u>
	<u>2536-07-4</u>					

L27 ANSWER 7 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

Full
Text

AN CA63:1790e CAOLD

TI 5-methyloxazolidine derivs.

PA Chemische Werke Albert

DT Patent

PATENT NO.	KIND	DATE
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PI BE 643289

FR M3206

IT	<u>1750-37-4</u>	<u>1750-38-5</u>	<u>1963-13-9</u>	<u>1969-12-6</u>	<u>2318-76-5</u>	<u>31788-64-4</u>
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L27 ANSWER 8 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

AN CA63:713h CAOLD

TI dry spinning of acetate fibers - (I) viscosity of the spinning solns.

AU Kamiya, Takuro; Hirokawa, K.

TI processing synthetic fibers

AU Usenko, V. A.

IT	<u>1533-33-1</u>	<u>1533-35-3</u>	<u>1695-96-1</u>	<u>1702-39-2</u>		
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L27 ANSWER 9 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

Full
Text

AN CA62:16256d CAOLD

TI pyrazolopyrroles

AU Grandberg, I. I.

DT Patent

PATENT NO. KIND DATE

PI SU 168299PI BE 654108FR 1415852

IT	<u>1058-48-6</u>	<u>1059-72-9</u>	<u>1107-42-2</u>	<u>1107-43-3</u>	<u>1107-45-5</u>	<u>1590-67-6</u>
	<u>1590-68-7</u>	<u>1590-73-4</u>	<u>1632-33-3</u>	<u>1806-69-5</u>	<u>1806-71-9</u>	<u>1806-72-0</u>
	<u>1806-73-1</u>	<u>1837-70-3</u>	<u>2046-36-8</u>	<u>2046-37-9</u>	<u>2046-39-1</u>	<u>2046-40-4</u>
	<u>2046-41-5</u>	<u>2046-43-7</u>	<u>2046-44-8</u>	<u>2046-92-6</u>	<u>2046-93-7</u>	<u>2046-94-8</u>
	<u>2048-43-3</u>	<u>2048-44-4</u>	<u>2048-45-5</u>	<u>2048-46-6</u>	<u>2048-57-9</u>	<u>2048-99-9</u>
	<u>2049-00-5</u>	<u>2049-01-6</u>	<u>2144-96-9</u>	<u>2144-97-0</u>	<u>2144-99-2</u>	<u>2145-00-8</u>
	<u>2145-01-9</u>	<u>2145-02-0</u>	<u>2235-84-9</u>	<u>2235-85-0</u>	<u>2311-90-2</u>	<u>2409-67-8</u>
	<u>2536-06-3</u>	<u>3141-57-9</u>	<u>3141-94-4</u>	<u>3141-95-5</u>	<u>3486-41-7</u>	<u>95445-05-9</u>

L27 ANSWER 10 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

Full
Text

AN CA62:1249g CAOLD

TI color correction in color photography

AU Magagnoli, Remo; Bellone, D.

PA Ferrania Societa per Azioni

DT Patent

PATENT NO. KIND DATE

PI DE 1168769IT 1533-32-0 1533-33-1 1702-39-2 2489-00-1

L27 ANSWER 11 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

Full
Text

AN CA62:681a CAOLD

TI couplers for photographic emulsion color development

AU Bellone, Domenico; Magagnoli, R.

PA Ferrania Societa per Azioni

DT Patent

PATENT NO. KIND DATE

PI DE 1150577

IT	<u>402-36-8</u>	<u>2489-27-2</u>	<u>2489-28-3</u>	<u>2489-29-4</u>	<u>2489-30-7</u>	<u>2489-31-8</u>
	<u>2489-54-5</u>	<u>2489-55-6</u>	<u>2489-56-7</u>	<u>2489-57-8</u>	<u>2489-58-9</u>	<u>2673-00-9</u>
	<u>2702-96-7</u>					

L27 ANSWER 12 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

Full
Text

AN CA60:702a CAOLD

TI heat-developable diazotype materials

AU Schaeffer, Andre

PA Etablissements Bauchet & Cie

DT Patent

PATENT NO. KIND DATE

PI FR 1325692

GB 1041022

IT 15006-70-9 58725-40-9 90230-09-4 94298-72-3 94489-23-3 95168-57-3
98564-39-7 100197-36-2 101174-68-9 103104-27-4 106041-87-6 106198-30-5
106951-55-7 107012-82-8 107541-74-2 107926-51-2

L27 ANSWER 13 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

Full
Text

AN CA60:701h CAOLD
 TI color couplers
 PA Ferrania Societa per Azioni
 DT Patent
 TI purple, photographic color coupler
 AU Bellone, Domenico; Magagnoli, R.
 DT Patent

PATENT NO.	KIND	DATE
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PI DE 1147483

IT 6752-38-1 92873-76-2

L27 ANSWER 14 OF 14 CAOLD COPYRIGHT 2004 ACS on STN

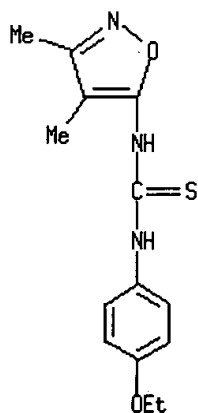
AN CA53:6122i CAOLD
 TI synthesis of asym. substituted derivs. of thiourea with potential
 tuberculostatic activity
 AU Oeriu, Simion; Voinescu, M.; Wexler, B.; Gloter, E.
 IT 1138-72-3 1142-30-9 100615-38-1 100720-16-9 100875-53-4 100875-54-5
101264-75-9 101872-56-4

=> fil reg; d acc 100720-16-9; fil CAOLD

FILE 'REGISTRY' ENTERED AT 21:18:21 ON 29 MAR 2004

ANSWER 1 REGISTRY COPYRIGHT 2004 ACS on STN

RN 100720-16-9 REGISTRY
 CN Urea, 1-(3,4-dimethyl-5-isoxazolyl)-3-(p-ethoxyphenyl)-2-thio- (6CI) (CA
 INDEX NAME)
 FS 3D CONCORD
 MF C14 H17 N3 O2 S
 SR CAOLD
 LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS
 (*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)
 1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

FILE 'CAOLD' ENTERED AT 21:18:42 ON 29 MAR 2004

=> fil reg; d acc 2048-43-3; fil CAOLD

FILE 'REGISTRY' ENTERED AT 21:19:20 ON 29 MAR 2004

ANSWER 1 REGISTRY COPYRIGHT 2004 ACS on STN

RN 2048-43-3 REGISTRY

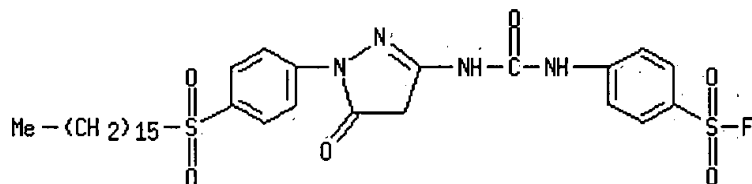
CN Sulfanilyl fluoride, N-[[1-[p-(hexadecylsulfonyl)phenyl]-5-oxo-2-pyrazolin-3-yl]carbamoyl]- (7CI, 8CI) (CA INDEX NAME)

FS 3D CONCORD

MF C32 H45 F N4 O6 S2

LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS

(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
 2 REFERENCES IN FILE CAPLUS (1907 TO DATE)
 2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

FILE 'CAOLD' ENTERED AT 21:19:21 ON 29 MAR 2004

=> fil reg; d acc 1963-13-9; fil CAOLD

FILE 'REGISTRY' ENTERED AT 21:19:46 ON 29 MAR 2004

ANSWER 1 REGISTRY COPYRIGHT 2004 ACS on STN

RN 1963-13-9 REGISTRY

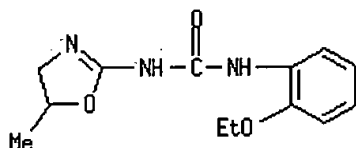
CN Urea, 1-(o-ethoxyphenyl)-3-(5-methyl-2-oxazolin-2-yl)- (7CI, 8CI) (CA INDEX NAME)

FS 3D CONCORD

MF C13 H17 N3 O3

LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS

(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
 2 REFERENCES IN FILE CAPLUS (1907 TO DATE)
 2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

FILE 'CAOLD' ENTERED AT 21:19:46 ON 29 MAR 2004

=> fil reg; d acc 1963-13-9; fil CAOLD

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.68	421.14
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-31.88

FILE 'REGISTRY' ENTERED AT 21:22:27 ON 29 MAR 2004

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 28 MAR 2004 HIGHEST RN 668418-93-7

DICTIONARY FILE UPDATES: 28 MAR 2004 HIGHEST RN 668418-93-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See [HELP CROSSOVER](#) for details.

Experimental and calculated property data are now available. For more information enter [HELP PROP](#) at an arrow prompt in the file or refer to the file summary sheet on the web at:

<http://www.cas.org/ONLINE/DBSS/registryss.html>

ANSWER 1 REGISTRY COPYRIGHT 2004 ACS on STN

RN 1963-13-9 REGISTRY

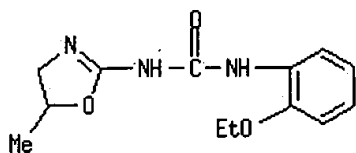
CN Urea, 1-(o-ethoxyphenyl)-3-(5-methyl-2-oxazolin-2-yl)- (7CI, 8CI) (CA INDEX NAME)

FS 3D CONCORD

MF C13 H17 N3 O3

LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS

(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

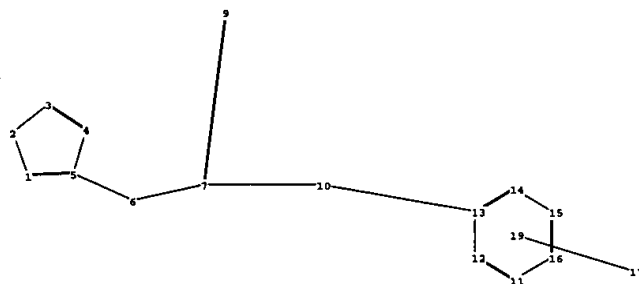
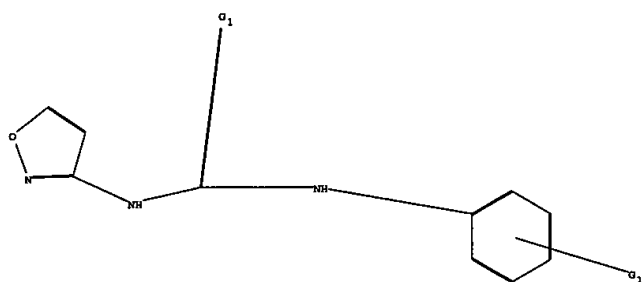
2 REFERENCES IN FILE CA (1907 TO DATE)
 2 REFERENCES IN FILE CAPLUS (1907 TO DATE)
 2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

FILE 'CAOLD' ENTERED AT 21:22:27 ON 29 MAR 2004

=> log y

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	0.42	423.75
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	0.00	-31.88

STN INTERNATIONAL LOGOFF AT 21:22:39 ON 29 MAR 2004



chain nodes :

6 7 9 10 17

ring nodes :

1 2 3 4 5 11 12 13 14 15 16

chain bonds :

5-6 6-7 7-9 7-10 10-13

ring bonds :

1-2 1-5 2-3 3-4 4-5 11-12 11-16 12-13 13-14 14-15 15-16

exact/norm bonds :

1-5 5-6 6-7 7-9 7-10 10-13

exact bonds :

1-2 2-3 3-4 4-5

normalized bonds :

11-12 11-16 12-13 13-14 14-15 15-16

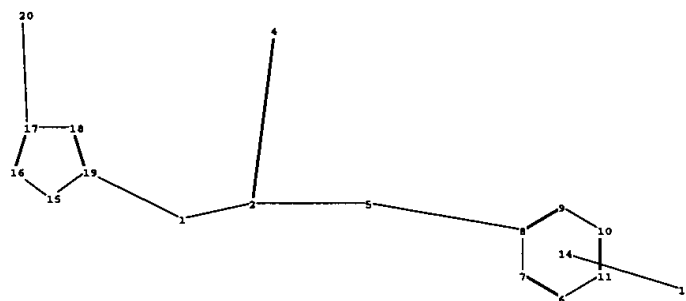
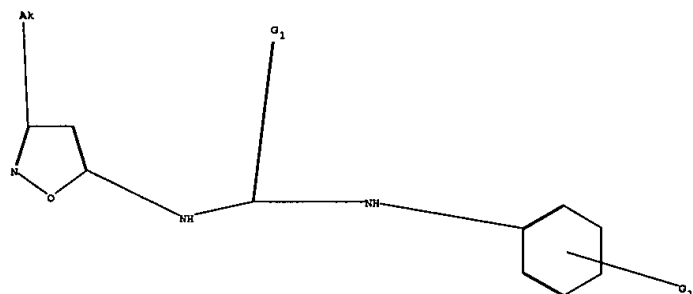
isolated ring systems :

containing 1 :

G1:O,S

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:CLASS 9:CLASS 10:CLASS 11:Atom
12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:CLASS 19:CLASS



chain nodes :

1 2 4 5 12 20

ring nodes :

6 7 8 9 10 11 15 16 17 18 19

chain bonds :

1-2 1-19 2-4 2-5 5-8 17-20

ring bonds :

6-7 6-11 7-8 8-9 9-10 10-11 15-16 15-19 16-17 17-18 18-19

exact/norm bonds :

1-2 1-19 2-4 2-5 5-8 16-17 17-20

exact bonds :

15-16 15-19 17-18 18-19

normalized bonds :

6-7 6-11 7-8 8-9 9-10 10-11

isolated ring systems :

containing 6 : 15 :

G1:O,S

Match level :

1:CLASS 2:CLASS 4:CLASS 5:CLASS 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
12:CLASS 14:CLASS 15:Atom 16:Atom 17:Atom 18:Atom 19:CLASS 20:CLASS

* * * * * Welcome to STN International * * * * *

<u>NEWS 1</u>		Web Page URLs for STN Seminar Schedule - N. America
<u>NEWS 2</u>		"Ask CAS" for self-help around the clock
<u>NEWS 3</u>	SEP 09	CA/CAPLUS records now contain indexing from 1907 to the present
<u>NEWS 4</u>	DEC 08	INPADOC: Legal Status data reloaded
<u>NEWS 5</u>	SEP 29	DISSABS now available on STN
<u>NEWS 6</u>	OCT 10	PCTFULL: Two new display fields added
<u>NEWS 7</u>	OCT 21	BIOSIS file reloaded and enhanced
<u>NEWS 8</u>	OCT 28	BIOSIS file segment of TOXCENTER reloaded and enhanced
<u>NEWS 9</u>	NOV 24	MSDS-CCOHS file reloaded
<u>NEWS 10</u>	DEC 08	CABA reloaded with left truncation
<u>NEWS 11</u>	DEC 08	IMS file names changed
<u>NEWS 12</u>	DEC 09	Experimental property data collected by CAS now available in REGISTRY
<u>NEWS 13</u>	DEC 09	STN Entry Date available for display in REGISTRY and CA/CAPLUS
<u>NEWS 14</u>	DEC 17	DGENE: Two new display fields added
<u>NEWS 15</u>	DEC 18	BIOTECHNO no longer updated
<u>NEWS 16</u>	DEC 19	CROPU no longer updated; subscriber discount no longer available
<u>NEWS 17</u>	DEC 22	Additional INPI reactions and pre-1907 documents added to CAS databases
<u>NEWS 18</u>	DEC 22	IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields
<u>NEWS 19</u>	DEC 22	ABI-INFORM now available on STN
<u>NEWS 20</u>	JAN 27	Source of Registration (SR) information in REGISTRY updated and searchable
<u>NEWS 21</u>	JAN 27	A new search aid, the Company Name Thesaurus, available in CA/CAPLUS
<u>NEWS 22</u>	FEB 05	German (DE) application and patent publication number format changes
<u>NEWS 23</u>	MAR 03	MEDLINE and LMEDLINE reloaded
<u>NEWS 24</u>	MAR 03	MEDLINE file segment of TOXCENTER reloaded
<u>NEWS 25</u>	MAR 03	FRANCEPAT now available on STN
<u>NEWS 26</u>	MAR 29	Pharmaceutical Substances (PS) now available on STN
<u>NEWS 27</u>	MAR 29	WPIFV now available on STN
<u>NEWS 28</u>	MAR 29	No connect hour charges in WPIFV until May 1, 2004
<u>NEWS 29</u>	MAR 29	New monthly current-awareness alert (SDI) frequency in RAPRA
<u>NEWS EXPRESS</u>		MARCH 5 CURRENT WINDOWS VERSION IS V7.00A, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 3 MARCH 2004
<u>NEWS HOURS</u>		STN Operating Hours Plus Help Desk Availability
<u>NEWS INTER</u>		General Internet Information
<u>NEWS LOGIN</u>		Welcome Banner and News Items
<u>NEWS PHONE</u>		Direct Dial and Telecommunication Network Access to STN
<u>NEWS WWW</u>		CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * STN Columbus * * * * *

FILE 'HOME' ENTERED AT 23:30:16 ON 29 MAR 2004

```
=> file reg
COST IN U.S. DOLLARS          SINCE FILE      TOTAL
                               ENTRY      SESSION
FULL ESTIMATED COST          0.21        0.21
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FILE 'REGISTRY' ENTERED AT 23:30:21 ON 29 MAR 2004
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Property values tagged with IC are from the ZIC/VINITI data file
 provided by InfoChem.

STRUCTURE FILE UPDATES: 28 MAR 2004 HIGHEST RN 668418-93-7
 DICTIONARY FILE UPDATES: 28 MAR 2004 HIGHEST RN 668418-93-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when
 conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

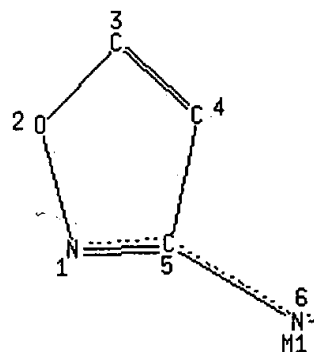
Experimental and calculated property data are now available. For more
 information enter HELP PROP at an arrow prompt in the file or refer
 to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

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=>
L1      STRUCTURE UPLOADED
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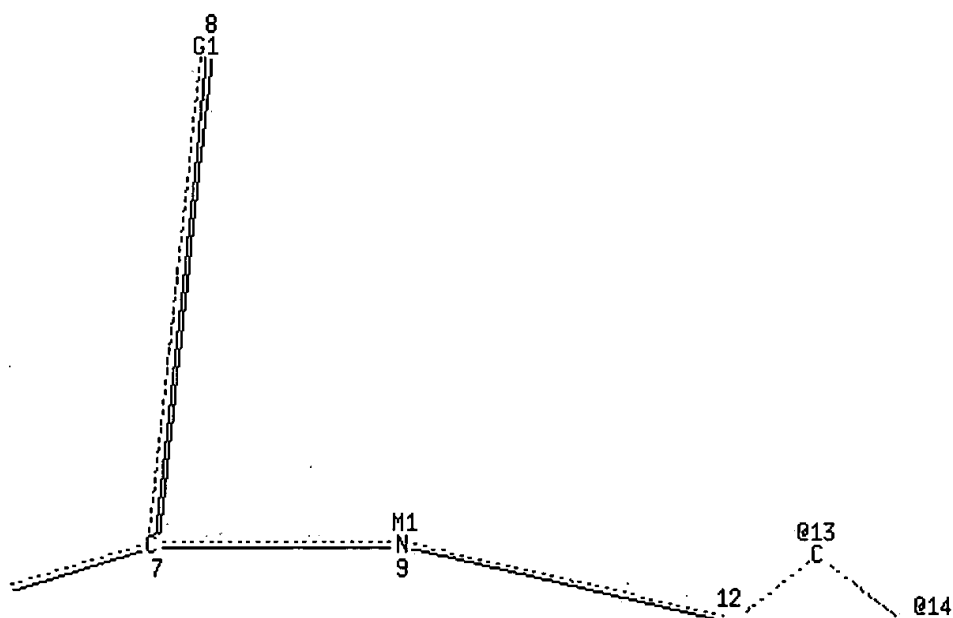
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=> 11
L1 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).
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=> d 11
L1 HAS NO ANSWERS
L1      STR
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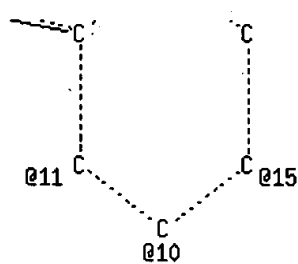
0 17 S 18



Page 1-A



Page 1-B



Page 2-B

G1 @16

Page 2-C

VAR G1=17/18

VPA 16-10/11/13/14/15 S

NODE ATTRIBUTES:

HCOUNT IS M1 AT 6
 HCOUNT IS M1 AT 9
 NSPEC IS R AT 1
 NSPEC IS R AT 2
 NSPEC IS R AT 3
 NSPEC IS R AT 4
 NSPEC IS R AT 5
 NSPEC IS C AT 6
 NSPEC IS C AT 7
 NSPEC IS C AT 8
 NSPEC IS C AT 9
 NSPEC IS R AT 10
 NSPEC IS R AT 11
 NSPEC IS R AT 12
 NSPEC IS R AT 13
 NSPEC IS R AT 14
 NSPEC IS R AT 15
 NSPEC IS C AT 16
 DEFAULT MLEVEL IS ATOM
 MLEVEL IS CLASS AT 6 7 9 17 18
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RSPEC 5
 NUMBER OF NODES IS 18

STEREO ATTRIBUTES: NONE

=> s 11

SAMPLE SEARCH INITIATED 23:32:27 FILE 'REGISTRY'
 SAMPLE SCREEN SEARCH COMPLETED - 50 TO ITERATE

100.0% PROCESSED 50 ITERATIONS 15 ANSWERS
 SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
 BATCH **COMPLETE**
 PROJECTED ITERATIONS: 576 TO 1424
 PROJECTED ANSWERS: 68 TO 532

L2 15 SEA SSS SAM L1

=> s 11 full

THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
 DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
 FULL SEARCH INITIATED 23:32:31 FILE 'REGISTRY'
 FULL SCREEN SEARCH COMPLETED - 845 TO ITERATE

100.0% PROCESSED 845 ITERATIONS 238 ANSWERS
 SEARCH TIME: 00.00.01

L3 238 SEA SSS FUL L1

=> file hcaplus

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	156.68	156.89

FILE 'HCAPLUS' ENTERED AT 23:32:34 ON 29 MAR 2004
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FILE COVERS 1907 - 29 Mar 2004 VOL 140 ISS 14
 FILE LAST UPDATED: 28 Mar 2004 (20040328/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 13

L4 11 L3

=> s 14 and dumas, j?/au

665 DUMAS, J?/AU

L5 2 L4 AND DUMAS, J?/AU

=> d 15, ibib abs fhitstr, 1-2

L5 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
--------------	----------------------

ACCESSION NUMBER: 1999:425745 HCAPLUS
 DOCUMENT NUMBER: 131:87909
 TITLE: Inhibition of p38 kinase activity using substituted heterocyclic ureas
 INVENTOR(S): Dumas, Jacques; Khire, Uday; Lowinger, Timothy Bruno; Paulsen, Holger; Riedl, Bernd; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia; Johnson, Jeffrey; Lee, Wendy; Redman, Aniko
 PATENT ASSIGNEE(S): Bayer Corporation, USA
 SOURCE: PCT Int. Appl., 126 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932111	A1	19990701	WO 1998-US26080	19981222
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,			

FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

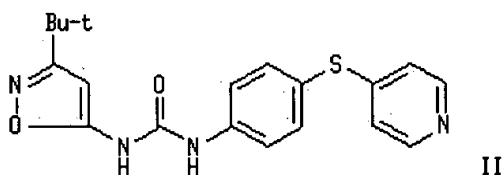
CA 2315720	AA	19990701	CA 1998-2315720	19981222
AU 9919971	A1	19990712	AU 1999-19971	19981222
AU 739642	B2	20011018		
EP 1041982	A1	20001011	EP 1998-964709	19981222

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO

JP 2001526223	T2	20011218	JP 2000-525102	19981222
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PRIORITY APPLN. INFO.: US 1997-995750 A 19971222
WO 1998-US26080 W 19981222

OTHER SOURCE(S): MARPAT 131:87909
GI



AB A method for treatment of p38-mediated disease other than cancer comprises administration of ANHCONHB [I; A = substituted isoxazolyl, pyrazolyl, thienyl, furyl; B = (substituted) mono-, di-, or tricyclic aryl, heteroaryl contg. ≥ 1 5-6 membered arom. structure contg. 0-4 N, O, or S atoms]. Reaction of 4-(4-pyridinylthio)aniline with 3-tert-butyl-5-isoxazolyl isocyanate in toluene gave title compd. II. In an in vitro p38 kinase assay, I displayed IC₅₀ values of 1-10 μ M.

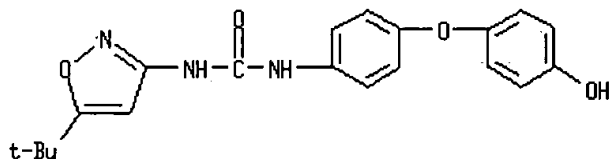
IT 228999-08-4P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(prepn. of substituted heterocyclic ureas for treatment of p38 kinase-mediated diseases other than cancer)

RN 228999-08-4 HCAPLUS

CN Urea, N-[5-(1,1-dimethylethyl)-3-isoxazolyl]-N'-[4-(4-hydroxyphenoxy)phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full
Text

Citing
References

ACCESSION NUMBER: 1999:425740 HCAPLUS

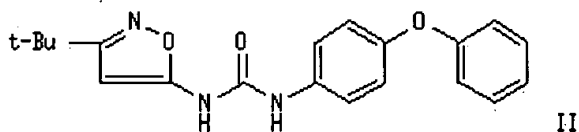
DOCUMENT NUMBER: 131:73648

TITLE: Inhibition of raf kinase using substituted heterocyclic ureas

INVENTOR(S): Dumas, Jacques; Khire, Uday; Lowinger, Timothy
Bruno; Paulsen, Holger; Riedl, Bernd; Scott, William

J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia; Johnson, Jeffrey; Lee, Wendy; Redman, Aniko
 PATENT ASSIGNEE(S): Bayer Corporation, USA
 SOURCE: PCT Int. Appl., 163 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932106	A1	19990701	WO 1998-US26078	19981222
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2315717	AA	19990701	CA 1998-2315717	19981222
AU 9921989	A1	19990712	AU 1999-21989	19981222
EP 1047418	A1	20001102	EP 1998-965981	19981222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001526220	T2	20011218	JP 2000-525097	19981222
BR 9814374	A	20020514	BR 1998-14374	19981222
NO 2000003232	A	20000821	NO 2000-3232	20000621
BG 104597	A	20010228	BG 2000-104597	20000712
PRIORITY APPLN. INFO.:			US 1997-996343	A 19971222
			WO 1998-US26078	W 19981222
OTHER SOURCE(S):		MARPAT 131:73648		
GI				

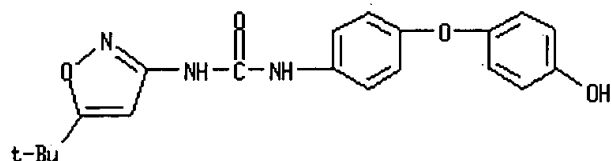


AB A method for treatment of cancerous cell growth mediated by raf kinase comprises administration of urea derivs. ANHCONHB [I; A = substituted isoxazolyl, thienyl, thiadiazolyl, furyl, pyrazolyl, etc.; B = (substituted) mono-, di-, or tricyclic aryl, heteroaryl contg. ≥ 1 5-6 membered arom. structure contg. 0-4 N, O, or S atoms]. Reaction of 4-phenyloxyphenyl isocyanate with 5-amino-3-tert-butylisoxazole in methylene chloride and heating at reflux temp. for 2 days gave title compd. II. In an in vitro raf kinase assay, I displayed IC₅₀ values of 1-10 μ M.

IT **228999-08-4P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
 (prepn. of substituted heterocyclic ureas for treatment of cancerous cell growth mediated by raf kinase)

RN 228999-08-4 HCAPLUS
 CN Urea, N-[5-(1,1-dimethylethyl)-3-isoxazolyl]-N'-[4-(4-hydroxyphenoxy)phenyl]-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 23:30:16 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 23:30:21 ON 29 MAR 2004

L1 STRUCTURE UPLOADED

L2 15 S L1

L3 238 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 23:32:34 ON 29 MAR 2004

L4 11 S L3

L5 2 S L4 AND DUMAS, J?/AU

=> s 14 not 15

L6 9 L4 NOT L5

=> d 16 and khire, u?/au

'U?' MUST END IN '/Q', '/A', '/L', '/S' OR '/B'

The saved name for a query (or structure or screen set) must end with '/Q'. The saved name for an answer set must end with '/A'. The saved name for an L# list must end with '/L'. SDI request names must end with '/S'. To see a list of all saved query, answer set,, and L# list names for this loginid, enter "DISPLAY SAVED" at an arrow prompt (=>). Enter "DISPLAY SAVED/S" to see a list of SDI request names. Enter "DISPLAY SAVED/B" to see a list of BATCH search requests.

=> s 16 and khire, u?/au

40 KHIRE, U?/AU

L7 0 L6 AND KHIRE, U?/AU

=> s 16 and lowinger, t?/au

41 LOWINGER, T?/AU

L8 1 L6 AND LOWINGER, T?/AU

=> d 18, ibib abs fhitstr, 1

L8 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2001:746592 HCAPLUS

DOCUMENT NUMBER: 136:95577

TITLE: Discovery of heterocyclic ureas as a new class of raf kinase inhibitors: identification of a second generation lead by a combinatorial chemistry approach

AUTHOR(S): Smith, R. A.; Barbosa, J.; Blum, C. L.; Bobko, M. A.; Caringal, Y. V.; Dally, R.; Johnson, J. S.; Katz, M. E.; Kennure, N.; Kingery-Wood, J.; Lee, W.; Lowinger, T. B.; Lyons, J.; Marsh, V.; Rogers, D. H.; Swartz, S.; Walling, T.; Wild, H.

CORPORATE SOURCE: Department of Chemistry Research, Bayer Research Center, West Haven, CT, 06516, USA

SOURCE: Bioorganic & Medicinal Chemistry Letters (2001), 11(20), 2775-2778
CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

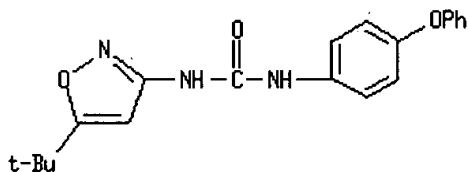
LANGUAGE: English

AB Heterocyclic ureas, such as N-3-thienyl N'-aryl ureas, have been identified as novel inhibitors of raf kinase, a key mediator in the ras signal transduction pathway. Structure-activity relationships were established, and the potency of the screening hit was improved 10-fold to $IC_{50}=1.7 \mu M$. A combinatorial synthesis approach enabled the identification of a breakthrough lead ($IC_{50}=0.54 \mu M$) for a second generation series of heterocyclic urea raf kinase inhibitors.

IT 228998-90-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(heterocyclic ureas as raf kinase inhibitors)

RN 228998-90-1 HCAPLUS

CN Urea, N-[5-(1,1-dimethylethyl)-3-isoxazolyl]-N'-(4-phenoxyphenyl)- (9CI)
(CA INDEX NAME)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 23:30:16 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 23:30:21 ON 29 MAR 2004

L1 STRUCTURE UPLOADED
L2 15 S L1
L3 238 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 23:32:34 ON 29 MAR 2004

L4 11 S L3
L5 2 S L4 AND DUMAS, J?/AU
L6 9 S L4 NOT L5
L7 0 S L6 AND KHIRE, U?/AU
L8 1 S L6 AND LOWINGER, T?/AU

=> s 16 not 18

L9 8 L6 NOT L8

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=> s 19 and paulsen, h?/au
      660 PAULSEN, H?/AU
L10      0 L9 AND PAULSEN, H?/AU

=> s 19 and riedl, b?/au
      163 RIEDL, B?/AU
L11      0 L9 AND RIEDL, B?/AU

=> s 19 and scott, w?/au
      1938 SCOTT, W?/AU
L12      0 L9 AND SCOTT, W?/AU

=> s 19 and smith, r?/au
      13384 SMITH, R?/AU
L13      0 L9 AND SMITH, R?/AU

=> s 19 and wood, j?/au
      3848 WOOD, J?/AU
L14      0 L9 AND WOOD, J?/AU

=> s 19 and hatoum-mokdad, h?/au
      26 HATOUM-MOKDAD, H?/AU
L15      0 L9 AND HATOUM-MOKDAD, H?/AU

=> s 19 and johnson, w?/au
      4424 JOHNSON, W?/AU
L16      0 L9 AND JOHNSON, W?/AU

=> s 19 and lee, w?/au
      8564 LEE, W?/AU
L17      0 L9 AND LEE, W?/AU

=> s 19 and redman, a?/au
      30 REDMAN, A?/AU
L18      0 L9 AND REDMAN, A?/AU

=> s 19 and sibley, r?/au
      189 SIBLEY, R?/AU
L19      0 L9 AND SIBLEY, R?/AU

=> s 19 and renick, j?/au
      14 RENICK, J?/AU
L20      0 L9 AND RENICK, J?/AU

=> d his
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(FILE 'HOME' ENTERED AT 23:30:16 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 23:30:21 ON 29 MAR 2004

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L1      STRUCTURE UPLOADED
L2      15 S L1
L3      238 S L1 FULL
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FILE 'HCAPLUS' ENTERED AT 23:32:34 ON 29 MAR 2004

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L4      11 S L3
L5      2 S L4 AND DUMAS, J?/AU
L6      9 S L4 NOT L5
L7      0 S L6 AND KHIRE, U?/AU
L8      1 S L6 AND LOWINGER, T?/AU
L9      8 S L6 NOT L8
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L10      0 S L9 AND PAULSEN, H?/AU
L11      0 S L9 AND RIEDL, B?/AU
L12      0 S L9 AND SCOTT, W?/AU
L13      0 S L9 AND SMITH, R?/AU
L14      0 S L9 AND WOOD, J?/AU
L15      0 S L9 AND HATOUM-MOKDAD, H?/AU
L16      0 S L9 AND JOHNSON, W?/AU
L17      0 S L9 AND LEE, W?/AU
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L19      0 S L9 AND SIBLEY, R?/AU
L20      0 S L9 AND RENICK, J?/AU

```

```

=> d 19, ibib abs fhistr, 1-8
'FHISTR' IS NOT A VALID FORMAT FOR FILE 'HCAPLUS'

```

The following are valid formats:

```

ABS ----- GI and AB
ALL ----- BIB, AB, IND, RE
APPS ----- AI, PRAI
BIB ----- AN, plus Bibliographic Data and PI table (default)
CAN ----- List of CA abstract numbers without answer numbers
CBIB ----- AN, plus Compressed Bibliographic Data
DALL ----- ALL, delimited (end of each field identified)
DMAX ----- MAX, delimited for post-processing
FAM ----- AN, PI and PRAI in table, plus Patent Family data
FBIB ----- AN, BIB, plus Patent FAM
IND ----- Indexing data
IPC ----- International Patent Classifications
MAX ----- ALL, plus Patent FAM, RE
PATS ----- PI, SO
SAM ----- CC, SX, TI, ST, IT
SCAN ----- CC, SX, TI, ST, IT (random display, no answer numbers;
        SCAN must be entered on the same line as the DISPLAY,
        e.g., D SCAN or DISPLAY SCAN)
STD ----- BIB, IPC, and NCL

IABS ----- ABS, indented with text labels
IALL ----- ALL, indented with text labels
IBIB ----- BIB, indented with text labels
IMAX ----- MAX, indented with text labels
ISTD ----- STD, indented with text labels

OBIB ----- AN, plus Bibliographic Data (original)
OIBIB ----- OBIB, indented with text labels

SBIB ----- BIB, no citations
SIBIB ----- IBIB, no citations

HIT ----- Fields containing hit terms
HITIND ----- IC, ICA, ICI, NCL, CC and index field (ST and IT)
        containing hit terms
HITRN ----- HIT RN and its text modification
HITSTR ----- HIT RN, its text modification, its CA index name, and
        its structure diagram
HITSEQ ----- HIT RN, its text modification, its CA index name, its
        structure diagram, plus NTE and SEQ fields
FHITSTR ----- First HIT RN, its text modification, its CA index name, and
        its structure diagram
FHITSEQ ----- First HIT RN, its text modification, its CA index name, its

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structure diagram, plus NTE and SEQ fields
 KWIC ----- Hit term plus 20 words on either side
 OCC ----- Number of occurrence of hit term and field in which it occurs

To display a particular field or fields, enter the display field codes. For a list of the display field codes, enter HELP DFIELDS at an arrow prompt (=>). Examples of formats include: TI; TI,AU; BIB,ST; TI,IND; TI,SO. You may specify the format fields in any order and the information will be displayed in the same order as the format specification.

All of the formats (except for SAM, SCAN, HIT, HITIND, HITRN, HITSTR, FHITSTR, HITSEQ, FHITSEQ, KWIC, and OCC) may be used with DISPLAY ACC to view a specified Accession Number.
 ENTER DISPLAY FORMAT (BIB):end

=> d his

(FILE 'HOME' ENTERED AT 23:30:16 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 23:30:21 ON 29 MAR 2004

L1 STRUCTURE UPLOADED
 L2 15 S L1
 L3 238 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 23:32:34 ON 29 MAR 2004

L4 11 S L3
 L5 2 S L4 AND DUMAS, J?/AU
 L6 9 S L4 NOT L5
 L7 0 S L6 AND KHIRE, U?/AU
 L8 1 S L6 AND LOWINGER, T?/AU
 L9 8 S L6 NOT L8
 L10 0 S L9 AND PAULSEN, H?/AU
 L11 0 S L9 AND RIEDL, B?/AU
 L12 0 S L9 AND SCOTT, W?/AU
 L13 0 S L9 AND SMITH, R?/AU
 L14 0 S L9 AND WOOD, J?/AU
 L15 0 S L9 AND HATOUM-MOKDAD, H?/AU
 L16 0 S L9 AND JOHNSON, W?/AU
 L17 0 S L9 AND LEE, W?/AU
 L18 0 S L9 AND REDMAN, A?/AU
 L19 0 S L9 AND SIBLEY, R?/AU
 L20 0 S L9 AND RENICK, J?/AU

=> d 19, ibib abs fhitstr, 1-8

L9 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2004:182368 HCAPLUS
 TITLE: Three hybrid assay system for isolating ligand-binding polypeptides and for isolating small mol. ligands
 INVENTOR(S): Come, Jon H.; Becker, Frank; Kley, Nikolai A.; Reichel, Christoph
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 238 pp., Cont.-in-part of U.S. Ser. No. 91,177.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English

NO

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004043388	A1	20040304	US 2002-234985	20020903
US 2003165873	A1	20030904	US 2002-91177	20020304
<u>PRIORITY APPLN. INFO.:</u>				
			US 2001-272932P	P 20010302
			US 2001-278233P	P 20010323
			US 2001-329437P	P 20011015
			US 2002-91177	A2 20020304

AB The invention provides compns. and methods for isolating ligand-binding polypeptides for a user-specified ligand, and for isolating small mol. ligands for a user-specified target polypeptide using an improved class of hybrid ligand compds. Prepn. of compds., e.g a methotrexate moiety linked by a polyethylene glycol moiety to dexamethasone, is described.

IT INDEXING IN PROGRESS

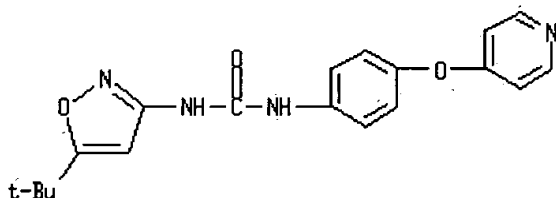
IT 228999-48-2D, conjugates

RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(three hybrid assay system for isolating ligand-binding polypeptides and for isolating small mol. ligands)

RN 228999-48-2 HCAPLUS

CN Urea, N-[5-(1,1-dimethylethyl)-3-isoxazolyl]-N'-[4-(4-pyridinyloxy)phenyl]-(9CI) (CA INDEX NAME)



L9 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2003:892762 HCAPLUS

DOCUMENT NUMBER: 139:395938

TITLE: Preparation of ureas as positive allosteric modulators of the nicotinic acetylcholine receptor

INVENTOR(S): Piotrowski, David W.; Rogers, Bruce N.; McWhorter, William W., Jr.; Walker, Daniel P.; Corbett, Jeffrey W.; Groppi, Vincent E., Jr.; Rudmann, Daniel G.

PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, USA

SOURCE: PCT Int. Appl., 159 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003093250	A2	20031113	WO 2003-US11493	20030428
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,				

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
 PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
 UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD,
 RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
 CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
 NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
 GW, ML, MR, NE, SN, TD, TG

US 2003236287 A1 20031225 US 2003-423062 20030425
 PRIORITY APPLN. INFO.: US 2002-377364P P 20020503
 US 2003-456941P P 20030324

OTHER SOURCE(S): MARPAT 139:395938

AB ANHCXNHB [X = O, S; A = (un)substituted Ph, 6-membered N heteroaryl; B =
 (un)substituted 5-6-membered heteroaryl] were prepd. to treat diseases or
 conditions in which the $\alpha 7$ nAChR is known to be involved (no data).
 Thus, 2,4-Me(MeO)C₆H₃NH₂ was treated with 3-F₃CC₆H₄CNO to give
 2,4-Me(MeO)C₆H₃NHCONHC₆H₄CF₃-3.

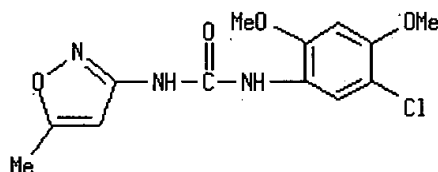
IT 501925-31-1P

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological
 study); PREP (Preparation); USES (Uses)

(prepn. of ureas as pos. allosteric modulators of the nicotinic
 acetylcholine receptor)

RN 501925-31-1 HCAPLUS

CN Urea, N-(5-chloro-2,4-dimethoxyphenyl)-N'-(5-methyl-3-isoxazolyl)- (9CI)
 (CA INDEX NAME)



L9 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2003:571600 HCAPLUS

DOCUMENT NUMBER: 140:59591

TITLE: Synthesis and biological activity of
 3-aryl-1-(5-methyl-4-acetyl-3-isoxazolyl)-2-thioxo-
 (1H,3H,5H)-pyrimidine-4,6-diones

AUTHOR(S): Swamy, S. Narasimha; Murthy, A. Krishna; Rajanarendar,
 E.

CORPORATE SOURCE: Department of Chemistry, Kakatiya University,
 Warangal, 506 009, India

SOURCE: Indian Journal of Heterocyclic Chemistry (2003),
 12(4), 357-360

CODEN: IJCHEI; ISSN: 0971-1627

PUBLISHER: Prof. R. S. Varma

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 3-Aryl-1-(5-methyl-4-acetyl-3-isoxazolyl)-2-thioxo-(1H,3H,5H)-pyrimidine-
 4,6-diones were prepd. by the interaction of 3-aryl-1-(5-methyl-3-
 isoxazolyl)thioureas with malonic acid in acetyl chloride. The
 3-isoxazolylthiourea compds. were made by the reaction of
 3-amino-5-methylisoxazole with aryl-isothiocyanates. Antibacterial and
 antifungal activity of 3-isoxazolylthiourea and 3-isoxazolyl-2-thioxo-
 (1H,3H,5H)-pyrimidine-4,6-diones compds. were studied.

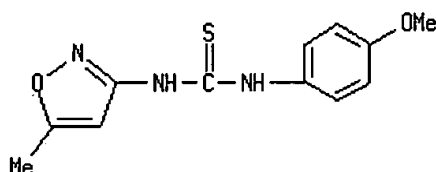
IT 638164-94-0P

RL: BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)

(antibacterial and antifungal activities; prepn. and biol. activity of 3-aryl-1-(5-methyl-3-isoxazolyl)thioureas and 3-aryl-1-(5-methyl-4-acetyl-3-isoxazolyl)-2-thioxo-(1H,3H,5H)-pyrimidine-4,6-diones)

RN 638164-94-0 HCAPLUS

CN Thiourea, N-(4-methoxyphenyl)-N'-(5-methyl-3-isoxazolyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2003:282524 HCAPLUS

DOCUMENT NUMBER: 138:304064

TITLE: Preparation of phenylurea derivatives as vanilloid receptor agonists

INVENTOR(S): Matsumoto, Takahiro; Yamamoto, Masataka; Nagabukuro, Hiroshi; Mochizuki, Manabu

PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan

SOURCE: PCT Int. Appl., 293 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003029199	A1	20030410	WO 2002-JP9995	20020927
WO 2003029199	C2	20030925		

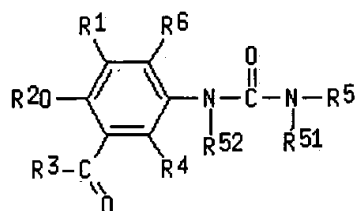
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 2001-300564 A 20010928

OTHER SOURCE(S): MARPAT 138:304064

GI



I

AB The title compds. I [R1, R4 and R6 are each independently hydrogen, halogeno, or hydrocarbyl; R2 is hydrocarbyl or a heterocyclic group; R3 is hydrocarbyl, etc.; R5 is hydrocarbyl or a heterocyclic group (except quinolyl) and R51 is hydrogen or hydrocarbyl, or R5 and R51 together with the nitrogen atom adjacent thereto may form a ring; and R52 is hydrogen or hydrocarbyl] are prepd. I are useful for the treatment of pain, urinary incontinence, etc. In a tail flick test using mice, one compd. of this invention showed a min. ED of 1 mg/kg.

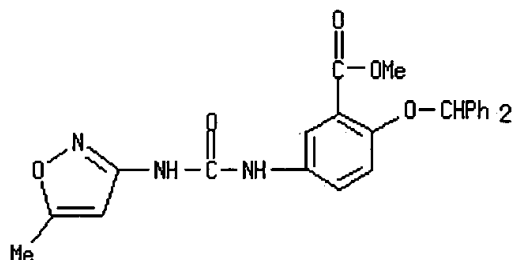
IT **508214-80-0P**

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of phenylurea derivs. as vanilloid receptor agonists)

RN **508214-80-0** HCAPLUS

CN Benzoic acid, 2-(diphenylmethoxy)-5-[[[(5-methyl-3-isoxazolyl)amino]carbonyl]amino]-, methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2002:849617 HCAPLUS

DOCUMENT NUMBER: 137:370101

TITLE: Preparation of quinoline derivatives having azolyl group and quinazoline derivatives as antitumor agents
INVENTOR(S): Kubo, Kazuo; Sakai, Teruyuki; Nagao, Rika; Fujiwara, Yasunari; Isoe, Toshiyuki; Hasegawa, Kazumasa

PATENT ASSIGNEE(S): Kirin Beer Kabushiki Kaisha, Japan

SOURCE: PCT Int. Appl., 89 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002088110	A1	20021107	WO 2002-JP4279	20020426

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

JP 2003012668	A2	20030115	JP 2002-126869	20020426
US 2003087907	A1	20030508	US 2002-132473	20020426
EP 1382604	A1	20040121	EP 2002-724651	20020426

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

NO 2003004595	A	20031219	NO 2003-4595	20031014
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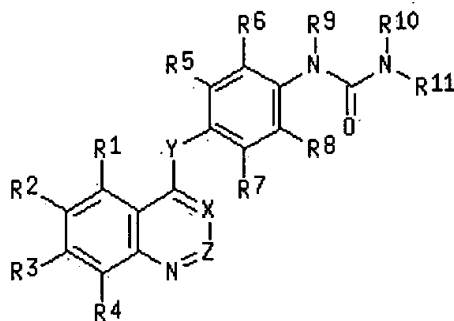
PRIORITY APPLN. INFO.:

JP 2001-132775	A	20010427
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WO 2002-JP4279	W	20020426
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OTHER SOURCE(S): MARPAT 137:370101

GI



I

AB N-[(4-quinolinyl or 4-quinazolinyl)thio or -oxy]phenyl-N'-azolyurea derivs. represented by the formula (I) or pharmaceutically acceptable salts or solvates thereof [wherein X, Z = CH, N; Y = O, S; R1, R2, R3 = H, NO2, NH2, each (un)substituted C1-6 alkyl or alkoxy or C2-6 alkenyl or alkynyl; R4 = H; R5-R8 = H, halo, C1-4 alkyl, alkoxy, or alkylthio, CF3, NO2, NH2; R9, R10 = C1-6 alkyl, each (un)substituted C1-4 alkylcarbonyl or C1-6 alkyl; R11 = (un)substituted azolyl] are prepd. These compds. are useful for the treatment of tumor, diabetic retinopathy, chronic articular rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma. They are also used for inhibiting neovascularization of a target blood vessel by contacting them with vascular endothelial cells of the target blood vessel. Thus, 100 mg 2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]aniline was dissolved in 5 mL CHCl3 and 0.5 mL Et3N, treated with a soln. of 100 mg triphosgene in CHCl3, and stirred at room temp. for 15 min, followed by adding 49 mg 2-aminothiazole, and the resulting mixt. was stirred at room temp. overnight to give 31 mg N-[2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl]-N'-(1,3-thiazol-2-yl)urea (II). II at 20 mg/kg/day for 9 days inhibited the growth of human lung cancer transplanted in nude mice by 92.0%. The compds. I in vitro showed IC50 of 0.001-0.0697 μ M for inhibiting the phosphorylation of the intracellular domain of human vascular endothelial cell growth factor (VEGF) receptor KDR (kinase insert domain-contg. receptor) in IH3T3 cell expressing human KDR.

IT 475108-15-7P, N-[3-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-N'-(3-isoxazolyl)urea

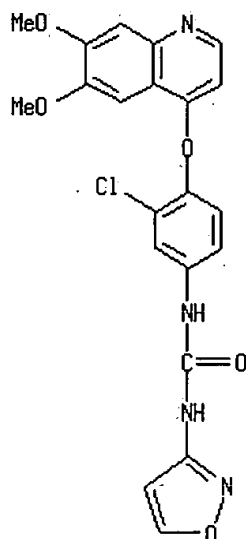
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU

(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of N-[(4-quinolinyl or 4-quinazolinyl)oxy]phenyl-N'-azolyurea derivs. as neovascularization inhibitors for treatment of tumor, diabetic retinopathy, chronic articular rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma)

RN 475108-15-7 HCAPLUS

CN Urea, N-[3-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-3-isoxazolyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2002:428885 HCAPLUS
 DOCUMENT NUMBER: 137:6179
 TITLE: Preparation of benzimidazoles as TIE-2 and/or VEGFR2 inhibitors
 INVENTOR(S): Cheung, Mui; Harris, Philip Anthony; Hasegawa, Masaichi; Ida, Satoru; Kano, Kazuya; Nishigaki, Naohiko; Sato, Hideyuki; Veal, James Martin; Washio, Yoshiaki; West, Rob I.
 PATENT ASSIGNEE(S): Glaxo Group Limited, UK; Glaxosmithkline K.K.
 SOURCE: PCT Int. Appl., 217 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002044156	A2	20020606	WO 2001-US44553	20011128
WO 2002044156	A3	20021017		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,

PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
 UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
 CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002032439 A5 20020611 AU 2002-32439 20011128

EP 1341771 A2 20030910 EP 2001-991963 20011128

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.:

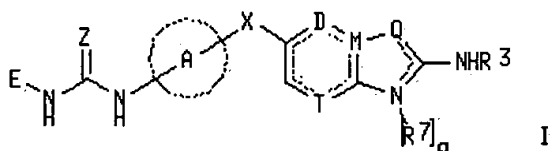
US 2000-253868P P 20001129

US 2001-310939P P 20010808

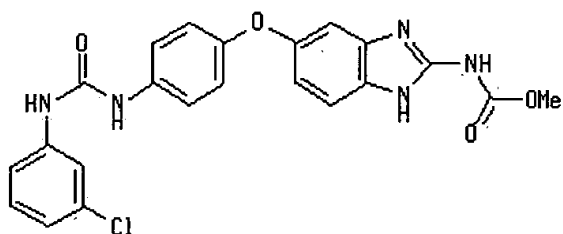
WO 2001-US44553 W 20011128

OTHER SOURCE(S): MARPAT 137:6179

GI



I



II

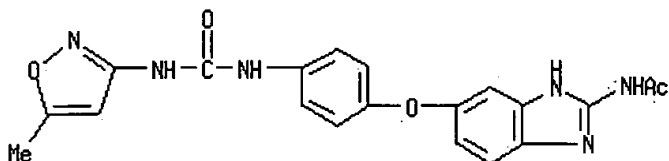
AB The title compds. [I; E = (un)substituted aryl, heteroaryl; A = aryl, heteroaryl, heterocyclyl; X = S, O, SO₂, SO, CH₂, CHOH, CO; Z = O, S; p = 0-1; q = 0-1; D = CH, T = CR₈, M = C and Q = NT₇p, wherein p = 0 and q = 1; or D = CH, T = CR₈, M = C and Q = NR₇p, wherein p = 1 and q = 0, or D = CH, T = CR₈, M = C and Q = S or O, wherein q = 0; or D = N, T = CR₈, M = C and Q = NR₇p, wherein either p or q = 0 and the other = 1; or D = CH, T = N, M = C and Q = NR₇p, wherein either p or q = 0 and the other = 1; or D = CH, T = CR₈, M = N and Q = CH, wherein q = 0; R₁ = alkyl, haloalkyl, aryl, etc.; R₂ = H, alkyl, aryl, etc.; R₃ = alkylene or alkylene substituted by oxo, and is linked together with N atom to which it is attached and to one of the benzimidazole N atoms to form a heterocyclic compd. fused to the benzimidazole; R₇ = H, alkyl, etc.; R₈ = H, halo] and their salts, useful in the treatment of hyperproliferative diseases, were prepd. Thus, reacting Me [5-(4-aminophenoxy)-1H-benzimidazol-2-yl]carbamate (prepn. given) with 3-chlorophenyl isocyanate in THF afforded 69% II which showed pIC₅₀ of > 7.0 in TIE-2 and VEGFR2 enzyme assays.

IT 433225-41-3P

RL: CPN (Combinatorial preparation); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); CMBI (Combinatorial study); PREP (Preparation); USES (Uses)
 (prepn. of benzimidazoles as TIE-2 and/or VEGFR2 inhibitors)

RN 433225-41-3 HCAPLUS

CN Acetamide, N-[5-[4-[[[(5-methyl-3-isoxazolyl)amino]carbonyl]amino]phenoxy]-1H-benzimidazol-2-yl]- (9CI) (CA INDEX NAME)



L9 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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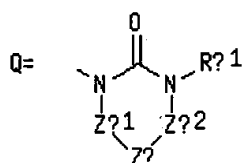
ACCESSION NUMBER: 2002:314913 HCAPLUS
 DOCUMENT NUMBER: 136:340689
 TITLE: Preparation of urea derivatives containing nitrogenous aromatic ring compounds as inhibitors of angiogenesis
 INVENTOR(S): Funahashi, Yasuhiro; Tsuruoka, Akihiko; Matsukura, Masayuki; Haneda, Toru; Fukuda, Yoshio; Kamata, Junichi; Takahashi, Keiko; Matsushima, Tomohiro; Miyazaki, Kazuki; Nomoto, Kenichi; Watanabe, Tatsuo; Obaishi, Hiroshi; Yamaguchi, Atsumi; Suzuki, Sachi; Nakamura, Katsuji; Mimura, Fusayo; Yamamoto, Yuji; Matsui, Junji; Matsui, Kenji; Yoshida, Takako; Suzuki, Yasuyuki; Arimoto, Itaru
 PATENT ASSIGNEE(S): Eisai Co., Ltd., Japan
 SOURCE: PCT Int. Appl., 699 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002032872	A1	20020425	WO 2001-JP9221	20011019
WO 2002032872	C1	20020926		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG AU 2001095986 A5 20020429 AU 2001-95986 20011019 NO 2003001731 A 20030619 NO 2003-1731 20030414 US 2004053908 A1 20040318 US 2003-420466 20030418				

PRIORITY APPLN. INFO.:

JP 2000-320420	A	20001020
JP 2000-386195	A	20001220
JP 2001-46685	A	20010222
WO 2001-JP9221	W	20011019

OTHER SOURCE(S): MARPAT 136:340689
 GI



AB N-aryl or N-heteroarylurea derivs. represented by the general formula Ag-Xg-Yg-Tg1 or salts thereof, or hydrates of both [wherein Ag = (un)substituted C6-14 aryl or 5- to 14-membered heterocyclic group; Xg = single bond, O, S, C1-6 alkylene, SO, SO₂, (un)substituted NH; Yg = (un)substituted C6-14 aryl, 5- to 14-membered heterocyclic group, C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl-C1-6 alkyl, 5- to 14-membered heteroaryl-C1-6 alkyl, (CH₂)_gSO₂ (g = 1-8), (CH₂)_{fa}CH:CH(CH₂)_{fb} (fa, fb = 0, 1, 2, 3), etc.; and Tg1 = a group of the general formula -Eg-CO-NRg1(Zg) or Q; wherein Eg = a single bond, (un)substituted NH; Rg1 = H, (un)substituted C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-8 aliph. hydrocarbyl, etc.; Zg = C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl, etc.; Zg1, Zg2 = (a) a single bond, (b) C1-6 alkylene optionally having ≥1 atoms selected from O, S, and N in the middle or the terminus of the chain and optionally substituted with oxo, (c) (un)substituted C2-6 alkenyl] are prepd. These compds. are also inhibitors of vascular endothelial growth factor receptor kinase (VEGFR2 kinase) and are useful as antitumor agents against hemangioma, pancreatic cancer, stomach cancer, colon cancer, breast cancer, prostate cancer, lung cancer, brain tumor, leukemia, or ovarian cancer, as cancer metastasis inhibitors, and for the treatment of retina neovascularization, diabetic retinopathy, atherosclerosis, or inflammatory diseases such as osteoarthritis, rheumatoid arthritis, psoriasis, or delayed hypersensitivity. Thus, to soln. of 334 mg 4-[6-(4-benzyloxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenylamine in 4 mL DMF were added 0.066 mL pyridine and 0.102 mL Ph chlorocarbonate and stirred at room temp. for 2.5 h to give 330 mg N-[4-[6-(4-benzyloxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea which (260 mg) was hydrogenolyzed over platinum oxide in ethanol overnight to give 160 mg N-[4-[6-(4-hydroxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea (I). I showed IC₅₀ of 0.02 nM for inhibiting the vascular endothelial growth factor (VEGF)-stimulated sandwich tube formation in vascular endothelial cell.

IT **417714-38-6P**

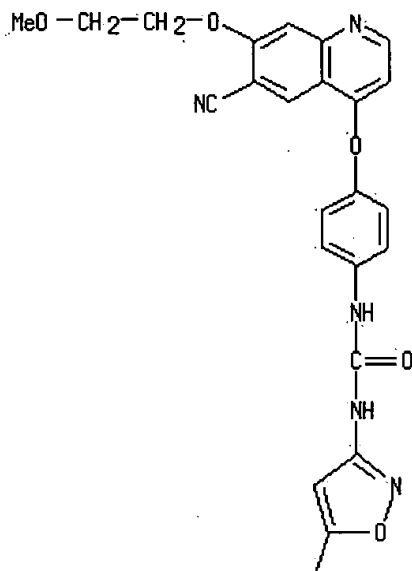
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of urea derivs. contg. nitrogenous arom. ring compds. as angiogenesis inhibitors for prevention or treatment of diseases)

RN **417714-38-6** HCAPLUS

CN Urea, N-[4-[[6-cyano-7-(2-methoxyethoxy)-4-quinolinyl]oxy]phenyl]-N'-(5-methyl-3-isoxazolyl)- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 1999:325902 HCAPLUS
 DOCUMENT NUMBER: 130:352546
 TITLE: Preparation of amides containing leucine or methionine for inhibition of the interaction of vascular cell-adhesion molecule-1 (VCAM-1) and fibronectin with integrin very late antigen 4 ($\alpha 4 \beta 1$)
 INVENTOR(S): Brittain, David Robert; Johnstone, Craig
 PATENT ASSIGNEE(S): Zeneca Limited, UK
 SOURCE: PCT Int. Appl., 74 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9924398	A2	19990520	WO 1998-GB3334	19981109
WO 9924398	A3	19990805		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2308716	AA	19990520	CA 1998-2308716	19981109
AU 9910420	A1	19990531	AU 1999-10420	19981109
EP 1030835	A2	20000830	EP 1998-952872	19981109
EP 1030835	B1	20030122		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

JP 2001522831	T2	20011120	JP 2000-520412	19981109
AT 231488	E	20030215	AT 1998-952872	19981109
ZA 9810330	A	19990512	ZA 1998-10330	19981111
NO 2000002158	A	20000711	NO 2000-2158	20000427
US 6344570	B1	20020205	US 2000-554224	20000711

PRIORITY APPLN. INFO.:

GB 1997-23789	A	19971112
WO 1998-GB3334	W	19981109

OTHER SOURCE(S): MARPAT 130:352546
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I; R1 = II (in the para or meta position); R2, R3 = H, NO₂, alkyl, etc.; R2 and R3 together with the Ph to which they are attached form a 9-10 membered bicyclic ring system; R4 = alkyl; R5 = H, alkyl; R6 = alkyl, alkylcycloalkyl, alkylalkoxyl, etc.; R7 = alkyl, alkoxycarbonyl, alkenyl, etc.; R8 = (un)substituted aryl, heteroaryl, bicyclic heteroaryl ring system linked to the nitrogen via a ring carbon, etc.; R9, R10 = H, alkyl; NR8R9 = dihydroindolyl, dihydroquinolinyl; R11 = CO₂H, tetrazolyl, alkyl sulfonylcarbonyl, sulfo, sulfinyl; Y = O, S, SO₂; m = 0-1; n = 0-4; with the proviso that when m and n cannot both be 0 and when m = 1, n = 0] and their pharmaceutically acceptable salts, useful in the treatment of multiple sclerosis, rheumatoid arthritis, asthma, coronary artery disease and psoriasis, were prepd. E.g., a multi-step synthesis of amide III was given. Compds. I are effective at 0.1-15 mg/kg/day.

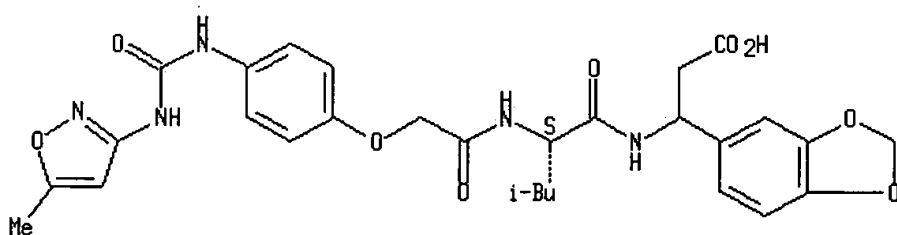
IT 225101-10-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of amides contg. leucine or methionine for inhibition of the interaction of vascular cell-adhesion mol.-1 (VCAM-1) and fibronectin with integrin very late antigen 4 ($\alpha 4 \beta 1$))

RN 225101-10-0 HCAPLUS

CN β -Alanine, N-[[4-[[[(5-methyl-3-isoxazolyl)amino]carbonyl]amino]phenoxy]acetyl]-L-leucyl-3-(1,3-benzodioxol-5-yl)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> file caold

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

	ENTRY	SESSION
FULL ESTIMATED COST	68.84	225.73
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	ENTRY	SESSION
CA SUBSCRIBER PRICE	-7.62	-7.62

FILE 'CAOLD' ENTERED AT 23:36:53 ON 29 MAR 2004
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FILE COVERS 1907-1966
 FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REGISTRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

=> d his

(FILE 'HOME' ENTERED AT 23:30:16 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 23:30:21 ON 29 MAR 2004

L1 STRUCTURE UPLOADED
 L2 15 S L1
 L3 238 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 23:32:34 ON 29 MAR 2004

L4 11 S L3
 L5 2 S L4 AND DUMAS, J?/AU
 L6 9 S L4 NOT L5
 L7 0 S L6 AND KHIRE, U?/AU
 L8 1 S L6 AND LOWINGER, T?/AU
 L9 8 S L6 NOT L8
 L10 0 S L9 AND PAULSEN, H?/AU
 L11 0 S L9 AND RIEDL, B?/AU
 L12 0 S L9 AND SCOTT, W?/AU
 L13 0 S L9 AND SMITH, R?/AU
 L14 0 S L9 AND WOOD, J?/AU
 L15 0 S L9 AND HATOUM-MOKDAD, H?/AU
 L16 0 S L9 AND JOHNSON, W?/AU
 L17 0 S L9 AND LEE, W?/AU
 L18 0 S L9 AND REDMAN, A?/AU
 L19 0 S L9 AND SIBLEY, R?/AU
 L20 0 S L9 AND RENICK, J?/AU

FILE 'CAOLD' ENTERED AT 23:36:53 ON 29 MAR 2004

=> s l3

L21 0 L3

=> file reg

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CA SUBSCRIBER PRICE	ENTRY	SESSION
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Property values tagged with IC are from the ZIC/VINITI data file
 provided by InfoChem.

STRUCTURE FILE UPDATES: 28 MAR 2004 HIGHEST RN 668418-93-7
 DICTIONARY FILE UPDATES: 28 MAR 2004 HIGHEST RN 668418-93-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when
 conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
 information enter HELP PROP at an arrow prompt in the file or refer
 to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

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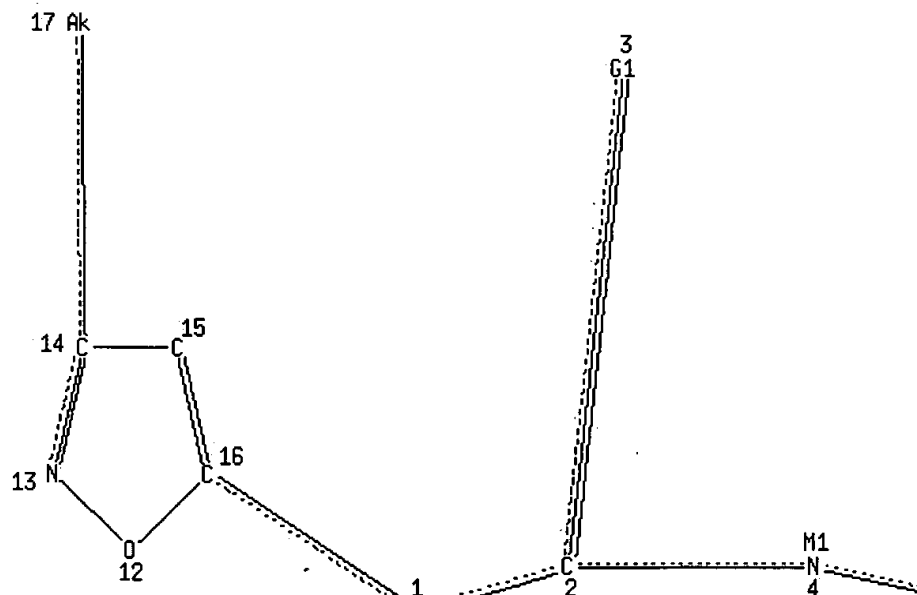
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L22 HAS NO ANSWERS

L22 STR

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Page 1-D



Page 1-E



Page 1-F

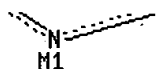
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O10

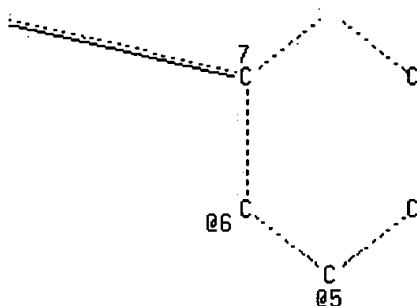
Page 2-A

G1 O11

Page 2-B



Page 2-E



Page 2-F

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VPA 11-5/6/8/9/10 S

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NSPEC	IS	C	AT	1
NSPEC	IS	C	AT	2
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NSPEC	IS	C	AT	17

DEFAULT MLEVEL IS ATOM

MLEVEL IS CLASS AT 1 2 4 16 17 18 19

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RSPEC I

NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE

=> s 122

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SAMPLE SCREEN SEARCH COMPLETED - 21 TO ITERATE

100.0% PROCESSED 21 ITERATIONS 4 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 146 TO 694
PROJECTED ANSWERS: 4 TO 200

L23 4 SEA SSS SAM L22

=> s 122 full

THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 23:38:37 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 506 TO ITERATE

100.0% PROCESSED 506 ITERATIONS 110 ANSWERS
SEARCH TIME: 00.00.01

L24 110 SEA SSS FUL L22

=> file hcaplus

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	ENTRY	SESSION
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	ENTRY	SESSION
CA SUBSCRIBER PRICE	0.00	-7.62

FILE 'HCAPLUS' ENTERED AT 23:38:41 ON 29 MAR 2004
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FILE COVERS 1907 - 29 Mar 2004 VOL 140 ISS 14
FILE LAST UPDATED: 28 Mar 2004 (20040328/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 124

L25 7 L24

=> s 125 and dumas, j?/au

665 DUMAS, J?/AU

L26 2 L25 AND DUMAS, J?/AU

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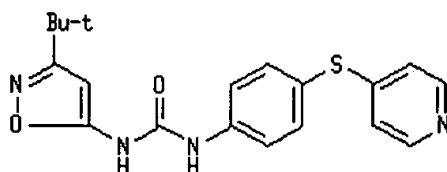
L26 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 1999:425745 HCAPLUS
DOCUMENT NUMBER: 131:87909
TITLE: Inhibition of p38 kinase activity using substituted heterocyclic ureas
INVENTOR(S): Dumas, Jacques; Khire, Uday; Lowinger, Timothy Bruno; Paulsen, Holger; Riedl, Bernd; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia; Johnson, Jeffrey; Lee, Wendy; Redman, Aniko
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: PCT Int. Appl., 126 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932111	A1	19990701	WO 1998-US26080	19981222
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2315720	AA	19990701	CA 1998-2315720	19981222
AU 9919971	A1	19990712	AU 1999-19971	19981222
AU 739642	B2	20011018		
EP 1041982	A1	20001011	EP 1998-964709	19981222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001526223	T2	20011218	JP 2000-525102	19981222
PRIORITY APPLN. INFO.:				
			US 1997-995750	A 19971222
			WO 1998-US26080	W 19981222

OTHER SOURCE(S): MARPAT 131:87909
GI



II

102 for Double Patenting

AB A method for treatment of p38-mediated disease other than cancer comprises

administration of ANHCONHB [I; A = substituted isoxazolyl, pyrazolyl, thienyl, furyl; B = (substituted) mono-, di-, or tricyclic aryl, heteroaryl contg. ≥ 1 5-6 membered arom. structure contg. 0-4 N, O, or S atoms]. Reaction of 4-(4-pyridinylthio)aniline with 3-tert-butyl-5-isoxazolyl isocyanate in toluene gave title compd. II. In an in vitro p38 kinase assay, I displayed IC50 values of 1-10 μ M.

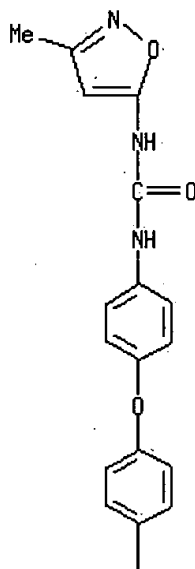
IT 229000-64-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of substituted heterocyclic ureas for treatment of p38 kinase-mediated diseases other than cancer)

RN 229000-64-0 HCAPLUS

CN Urea, N-(3-methyl-5-isoxazolyl)-N'-[4-(4-methylphenoxy)phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT.

L26 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 1999:425740 HCAPLUS

DOCUMENT NUMBER: 131:73648

TITLE: Inhibition of raf kinase using substituted heterocyclic ureas

INVENTOR(S): Dumas, Jacques; Khire, Uday; Lowinger, Timothy Bruno; Paulsen, Holger; Riedl, Bernd; Scott, William J.; Smith, Roger A.; Wood, Jill E.; Hatoum-Mokdad, Holia; Johnson, Jeffrey; Lee, Wendy; Redman, Aniko

PATENT ASSIGNEE(S): Bayer Corporation, USA

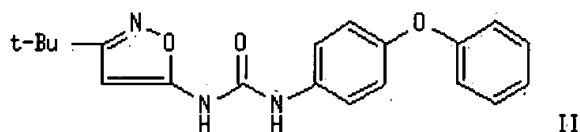
SOURCE: PCT Int. Appl., 163 pp.

CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932106	A1	19990701	WO 1998-US26078	19981222
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2315717	AA	19990701	CA 1998-2315717	19981222
AU 9921989	A1	19990712	AU 1999-21989	19981222
EP 1047418	A1	20001102	EP 1998-965981	19981222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001526220	T2	20011218	JP 2000-525097	19981222
BR 9814374	A	20020514	BR 1998-14374	19981222
NO 2000003232	A	20000821	NO 2000-3232	20000621
BG 104597	A	20010228	BG 2000-104597	20000712
PRIORITY APPLN. INFO.:		US 1997-996343 A 19971222		
		WO 1998-US26078 W 19981222		

OTHER SOURCE(S): MARPAT 131:73648

GI



AB A method for treatment of cancerous cell growth mediated by raf kinase comprises administration of urea derivs. ANHCONHB [I; A = substituted isoxazolyl, thienyl, thiadiazolyl, furyl, pyrazolyl, etc.; B = (substituted) mono-, di-, or tricyclic aryl, heteroaryl contg. ≥1 5-6 membered arom. structure contg. 0-4 N, O, or S atoms]. Reaction of 4-phenyloxyphenyl isocyanate with 5-amino-3-tert-butylisoxazole in methylene chloride and heating at reflux temp. for 2 days gave title compd. II. In an in vitro raf kinase assay, I displayed IC₅₀ values of 1-10 μM.

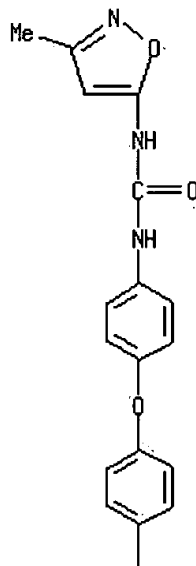
IT 229000-64-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of substituted heterocyclic ureas for treatment of cancerous cell growth mediated by raf kinase)

RN 229000-64-0 HCAPLUS

CN Urea, N-(3-methyl-5-isoxazolyl)-N'-[4-(4-methylphenoxy)phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT:

7

THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 23:30:16 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 23:30:21 ON 29 MAR 2004

L1 STRUCTURE UPLOADED

L2 15 S L1

L3 238 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 23:32:34 ON 29 MAR 2004

L4 11 S L3

L5 2 S L4 AND DUMAS, J?/AU

L6 9 S L4 NOT L5

L7 0 S L6 AND KHIRE, U?/AU

L8 1 S L6 AND LOWINGER, T?/AU

L9 8 S L6 NOT L8

L10 0 S L9 AND PAULSEN, H?/AU

L11 0 S L9 AND RIEDL, B?/AU

L12 0 S L9 AND SCOTT, W?/AU

L13 0 S L9 AND SMITH, R?/AU

L14 0 S L9 AND WOOD, J?/AU

L15 0 S L9 AND HATOUM-MOKDAD, H?/AU

L16 0 S L9 AND JOHNSON, W?/AU

L17 0 S L9 AND LEE, W?/AU

L18 0 S L9 AND REDMAN, A?/AU

L19 0 S L9 AND SIBLEY, R?/AU

L20 0 S L9 AND RENICK, J?/AU

FILE 'CAOLD' ENTERED AT 23:36:53 ON 29 MAR 2004

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L24          110 S L22 FULL

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=> s 125 not 126
L27          5 L25 NOT L26

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          40 KHIRI, U?/AU
L28          0 L27 AND KHIRI, U?/AU

=> s 127 and lowinger, t?/au
          41 LOWINGER, T?/AU
L29          0 L27 AND LOWINGER, T?/AU

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          660 PAULSEN, H?/AU
L30          0 L27 AND PAULSEN, H?/AU

=> s 127 and riedl, b?/au
          163 RIEDL, B?/AU
L31          0 L27 AND RIEDL, B?/AU

=> s 127 and scott, w?/au
          1938 SCOTT, W?/AU
L32          0 L27 AND SCOTT, W?/AU

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          13384 SMITH, R?/AU
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          3848 WOOD, J?/AU
L34          0 L27 AND WOOD, J?/AU

=> s 127 and hatoum-mokdad, h?/au
          26 HATOUM-MOKDAD, H?/AU
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          7564 JOHNSON, J?/AU
L36          0 L27 AND JOHNSON, J?/AU

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          8564 LEE, W?/AU
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          30 REDMAN, A?/AU
L38          0 L27 AND REDMAN, A?/AU

=> s 127 and sibley, r?/au
          189 SIBLEY, R?/AU

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14 RENICK, J?/AU

L40 0 L27 AND RENICK, J?/AU

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(FILE 'HOME' ENTERED AT 23:30:16 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 23:30:21 ON 29 MAR 2004

L1 STRUCTURE UPLOADED

L2 15 S L1

L3 238 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 23:32:34 ON 29 MAR 2004

L4 11 S L3

L5 2 S L4 AND DUMAS, J?/AU

L6 9 S L4 NOT L5

L7 0 S L6 AND KHIRE, U?/AU

L8 1 S L6 AND LOWINGER, T?/AU

L9 8 S L6 NOT L8

L10 0 S L9 AND PAULSEN, H?/AU

L11 0 S L9 AND RIEDL, B?/AU

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L13 0 S L9 AND SMITH, R?/AU

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L19 0 S L9 AND SIBLEY, R?/AU

L20 0 S L9 AND RENICK, J?/AU

FILE 'CAOLD' ENTERED AT 23:36:53 ON 29 MAR 2004

L21 0 S L3

FILE 'REGISTRY' ENTERED AT 23:37:00 ON 29 MAR 2004

L22 STRUCTURE UPLOADED

L23 4 S L22

L24 110 S L22 FULL

FILE 'HCAPLUS' ENTERED AT 23:38:41 ON 29 MAR 2004

L25 7 S L24

L26 2 S L25 AND DUMAS, J?/AU

L27 5 S L25 NOT L26

L28 0 S L27 AND KHIRE, U?/AU

L29 0 S L27 AND LOWINGER, T?/AU

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L38 0 S L27 AND REDMAN, A?/AU

L39 0 S L27 AND SIBLEY, R?/AU

L40 0 S L27 AND RENICK, J?/AU

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L27 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2004:182368 HCAPLUS
 TITLE: Three hybrid assay system for isolating ligand-binding polypeptides and for isolating small mol. ligands
 INVENTOR(S): Come, Jon H.; Becker, Frank; Kley, Nikolai A.; Reichel, Christoph
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 238 pp., Cont.-in-part of U.S. Ser. No. 91,177.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004043388	A1	20040304	US 2002-234985	20020903
US 2003165873	A1	20030904	US 2002-91177	20020304
PRIORITY APPLN. INFO.:				
			US 2001-272932P	P 20010302
			US 2001-278233P	P 20010323
			US 2001-329437P	P 20011015
			US 2002-91177	A2 20020304

AB The invention provides compns. and methods for isolating ligand-binding polypeptides for a user-specified ligand, and for isolating small mol. ligands for a user-specified target polypeptide using an improved class of hybrid ligand compds. Prepn. of compds., e.g a methotrexate moiety linked by a polyethylene glycol moiety to dexamethasone, is described.

IT INDEXING IN PROGRESS

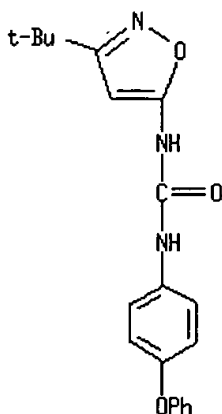
IT 229000-80-0D, conjugates

RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(three hybrid assay system for isolating ligand-binding polypeptides and for isolating small mol. ligands)

RN 229000-80-0 HCAPLUS

CN Urea, N-[3-(1,1-dimethylethyl)-5-isoxazolyl]-N'-(4-phenoxyphenyl)- (9CI)
 (CA INDEX NAME)

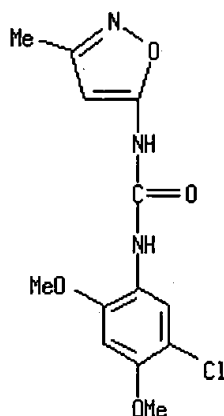


L27 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2003:892762 HCAPLUS
 DOCUMENT NUMBER: 139:395938
 TITLE: Preparation of ureas as positive allosteric modulators of the nicotinic acetylcholine receptor
 INVENTOR(S): Piotrowski, David W.; Rogers, Bruce N.; McWhorter, William W., Jr.; Walker, Daniel P.; Corbett, Jeffrey W.; Groppi, Vincent E., Jr.; Rudmann, Daniel G.
 PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, USA
 SOURCE: PCT Int. Appl., 159 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003093250	A2	20031113	WO 2003-US11493	20030428
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003236287	A1	20031225	US 2003-423062	20030425
PRIORITY APPLN. INFO.:			US 2002-377364P	P 20020503
			US 2003-456941P	P 20030324
OTHER SOURCE(S): MARPAT 139:395938				
AB ANHCXNHB [X = O, S; A = (un)substituted Ph, 6-membered N heteroaryl; B = (un)substituted 5-6-membered heteroaryl] were prepd. to treat diseases or conditions in which the $\alpha 7$ nAChR is known to be involved (no data). Thus, 2,4-Me(MeO)C ₆ H ₃ NH ₂ was treated with 3-F ₃ CC ₆ H ₄ CNO to give 2,4-Me(MeO)C ₆ H ₃ NHCONHC ₆ H ₄ CF ₃ -3.				
IT 625117-71-7P				
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (prepn. of ureas as pos. allosteric modulators of the nicotinic acetylcholine receptor)				
RN	625117-71-7 HCAPLUS			
CN	Urea, N-(5-chloro-2,4-dimethoxyphenyl)-N'-(3-methyl-5-isoxazolyl)- (9CI) (CA INDEX NAME)			

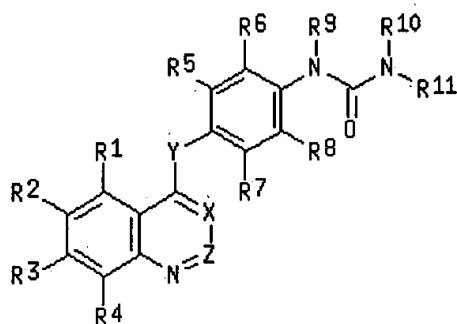


L27 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2002:849617 HCAPLUS
 DOCUMENT NUMBER: 137:370101
 TITLE: Preparation of quinoline derivatives having azolyl group and quinazoline derivatives as antitumor agents
 INVENTOR(S): Kubo, Kazuo; Sakai, Teruyuki; Nagao, Rika; Fujiwara, Yasunari; Iseo, Toshiyuki; Hasegawa, Kazumasa
 PATENT ASSIGNEE(S): Kirin Beer Kabushiki Kaisha, Japan
 SOURCE: PCT Int. Appl., 89 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002088110	A1	20021107	WO 2002-JP4279	20020426
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
JP 2003012668	A2	20030115	JP 2002-126869	20020426
US 2003087907	A1	20030508	US 2002-132473	20020426
EP 1382604	A1	20040121	EP 2002-724651	20020426
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
NO 2003004595	A	20031219	NO 2003-4595	20031014
PRIORITY APPLN. INFO.:			JP 2001-132775	A 20010427
			WO 2002-JP4279	W 20020426
OTHER SOURCE(S):			MARPAT 137:370101	
GI				



AB N-[(4-quinolinyl or 4-quinazolinyl)thio or -oxy]phenyl-N'-azolyurea derivs. represented by the formula (I) or pharmaceutically acceptable salts or solvates thereof [wherein X, Z = CH, N; Y = O, S; R1, R2, R3 = H, NO2, NH2, each (un)substituted C1-6 alkyl or alkoxy or C2-6 alkenyl or alkynyl; R4 = H; R5-R8 = H, halo, C1-4 alkyl, alkoxy, or alkylthio, CF3, NO2, NH2; R9, R10 = C1-6 alkyl, each (un)substituted C1-4 alkylcarbonyl or C1-6 alkyl; R11 = (un)substituted azoyl] are prepd. These compds. are useful for the treatment of tumor, diabetic retinopathy, chronic articular rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma. They are also used for inhibiting neovascularization of a target blood vessel by contacting them with vascular endothelial cells of the target blood vessel. Thus, 100 mg 2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]aniline was dissolved in 5 mL CHCl3 and 0.5 mL Et3N, treated with a soln. of 100 mg triphosgene in CHCl3, and stirred at room temp. for 15 min, followed by adding 49 mg 2-aminothiazole, and the resulting mixt. was stirred at room temp. overnight to give 31 mg N-[2-chloro-4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl]-N'-(1,3-thiazol-2-yl)urea (II). II at 20 mg/kg/day for 9 days inhibited the growth of human lung cancer transplanted in nude mice by 92.0%. The compds. I in vitro showed IC50 of 0.001-0.0697 μ M for inhibiting the phosphorylation of the intracellular domain of human vascular endothelial cell growth factor (VEGF) receptor KDR (kinase insert domain-contg. receptor) in IH3T3 cell expressing human KDR.

IT **475108-16-8P**, N-[3-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-N'-(3-methyl-5-isoxazolyl)urea

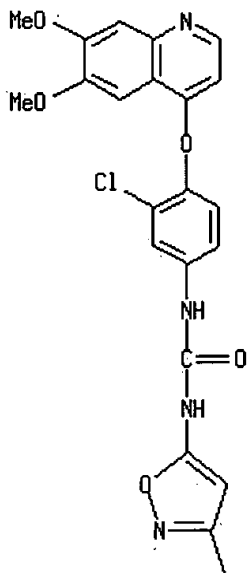
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of N-[(4-quinolinyl or 4-quinazolinyl)oxy]phenyl-N'-azolyurea derivs. as neovascularization inhibitors for treatment of tumor, diabetic retinopathy, chronic articular rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma)

RN **475108-16-8** HCAPLUS

CN Urea, N-[3-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(3-methyl-5-isoxazolyl)- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text	Citing References
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ACCESSION NUMBER: 2002:314913 HCAPLUS
 DOCUMENT NUMBER: 136:340689
 TITLE: Preparation of urea derivatives containing nitrogenous aromatic ring compounds as inhibitors of angiogenesis
 FUNAHASHI, Yasuhiro; TSURUOKA, Akihiko; MATSUKURA, Masayuki; HANEDA, Toru; FUKUDA, Yoshio; KAMATA, Junichi; TAKAHASHI, Keiko; MATSUSHIMA, Tomohiro; MIYAZAKI, Kazuki; NOMOTO, Kenichi; WATANABE, Tatsuo; OBAISHI, Hiroshi; YAMAGUCHI, Atsumi; SUZUKI, Sachi; NAKAMURA, Katsuji; MIMURA, Fusayo; YAMAMOTO, Yuji; MATSUI, Junji; MATSUI, Kenji; YOSHIBA, Takako; SUZUKI, Yasuyuki; ARIMOTO, Itaru
 PATENT ASSIGNEE(S): Eisai Co., Ltd., Japan
 SOURCE: PCT Int. Appl., 699 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002032872	A1	20020425	WO 2001-JP9221	20011019
WO 2002032872	C1	20020926		

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 PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
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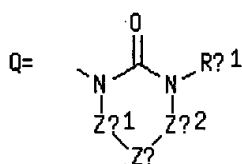
AU 2001095986	A5	20020429	AU 2001-95986	20011019
NO 2003001731	A	20030619	NO 2003-1731	20030414
US 2004053908	A1	20040318	US 2003-420466	20030418

PRIORITY APPLN. INFO.:

JP 2000-320420	A	20001020
JP 2000-386195	A	20001220
JP 2001-46685	A	20010222
WO 2001-JP9221	W	20011019

OTHER SOURCE(S): MARPAT 136:340689

GI



AB N-aryl or N-heteroarylurea derivs. represented by the general formula Ag-Xg-Yg-Tg1 or salts thereof, or hydrates of both [wherein Ag = (un)substituted C6-14 aryl or 5- to 14-membered heterocyclic group; Xg = single bond, O, S, C1-6 alkylene, SO, SO2, (un)substituted NH; Yg = (un)substituted C6-14 aryl, 5- to 14-membered heterocyclic group, C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl-C1-6 alkyl, 5- to 14-membered heteroaryl-C1-6 alkyl, (CH2)gSO2 (g = 1-8), (CH2)faCH:CH(CH2)fb (fa, fb = 0, 1, 2, 3), etc.; and Tg1 = a group of the general formula -Eg-CO-NRg1(Zg) or Q; wherein Eg = a single bond, (un)substituted NH; Rg1 = H, (un)substituted C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-8 aliph. hydrocarbyl, etc.; Zg = C1-8 alkyl, C3-8 alicyclic hydrocarbyl, C6-14 aryl, etc.; Zg1, Zg2 = (a) a single bond, (b) C1-6 alkylene optionally having ≥1 atoms selected from O, S, and N in the middle or the terminus of the chain and optionally substituted with oxo, (c) (un)substituted C2-6 alkenyl] are prepd. These compds. are also inhibitors of vascular endothelial growth factor receptor kinase (VEGFR2 kinase) and are useful as antitumor agents against hemangioma, pancreatic cancer, stomach cancer, colon cancer, breast cancer, prostate cancer, lung cancer, brain tumor, leukemia, or ovarian cancer, as cancer metastasis inhibitors, and for the treatment of retina neovascularization, diabetic retinopathy, atherosclerosis, or inflammatory diseases such as osteoarthritis, rheumatoid arthritis, psoriasis, or delayed hypersensitivity. Thus, to soln. of 334 mg 4-[6-(4-benzyloxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenylamine in 4 mL DMF were added 0.066 mL pyridine and 0.102 mL Ph chlorocarbonate and stirred at room temp. for 2.5 h to give 330 mg N-[4-[6-(4-benzyloxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea which (260 mg) was hydrogenolyzed over platinum oxide in ethanol overnight to give 160 mg N-[4-[6-(4-hydroxyphenyl)-7-(2-trimethylsilylethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]-2-chlorophenyl]-N'-cyclopropylurea (I). I showed IC50 of 0.02 nM for inhibiting the vascular endothelial growth factor (VEGF)-stimulated sandwich tube formation in vascular endothelial cell.

IT **417714-37-5P**

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU

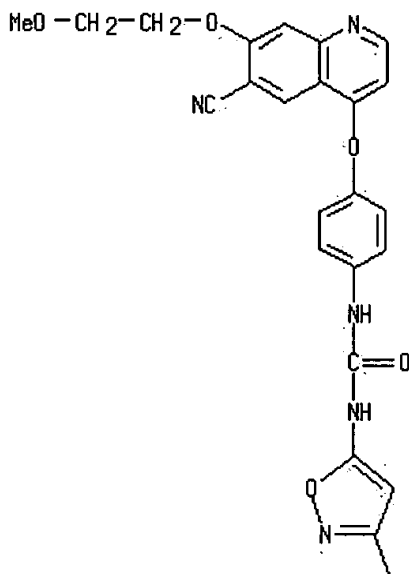
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of urea derivs. contg. nitrogenous arom. ring compds. as angiogenesis inhibitors for prevention or treatment of diseases)

RN 417714-37-5 HCAPLUS

CN Urea, N-[4-[[6-cyano-7-(2-methoxyethoxy)-4-quinolinyl]oxy]phenyl]-N'-(3-methyl-5-isoxazolyl)- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

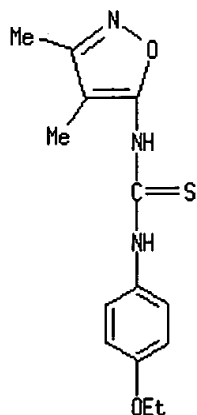
Full Text	Citing References
ACCESSION NUMBER:	1959:34516 HCAPLUS
DOCUMENT NUMBER:	53:34516
ORIGINAL REFERENCE NO.:	53:6122h-i, 6123a
TITLE:	Synthesis of several asymmetrically substituted derivatives of thiourea with potential tuberculostatic activity
AUTHOR(S):	Oeriv, S.; Voinescu, M.; Wexler, B.; Gloter, E.
SOURCE:	Acad. rep. populare Romine, Studii cercetari chim. (1958), 6, 155-60
DOCUMENT TYPE:	Journal
LANGUAGE:	Unavailable
AB	The following p-ROC6H4NHCSCH2CH:CH2 (R and m.p. given) were prepd. from CH2:CHCH2NCS and the corresponding p-ROC6H4NH2: Me, 78°; Et, 97°; CH2:CHCH2, 74°; Pr, 68°; Me2CHCH2, 105-6°; Bu, 84-5°; n-C8H17, 86-7°. Their tuberculostatic activity in vitro varied from a diln. of 1/180,000 to 1/1,800,000. N-(p-Ethoxyphenyl)-N'-(3,4-dimethyl-5-isoxazolyl)isothiurea, m. 171-2°, prepd. from p-EtOC6H4NCS and

3,4-dimethyl-5-aminoisoxazole, had an activity in vitro at a diln. of 1/10,000,000.

IT 100720-16-9, Urea, 1-(3,4-dimethyl-5-isoxazolyl)-3-(p-ethoxyphenyl)-2-thio-
(prepn. of)

RN 100720-16-9 HCAPLUS

CN Urea, 1-(3,4-dimethyl-5-isoxazolyl)-3-(p-ethoxyphenyl)-2-thio- (6CI) (CA
INDEX NAME)



=> d his

(FILE 'HOME' ENTERED AT 23:30:16 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 23:30:21 ON 29 MAR 2004

L1 STRUCTURE UPLOADED
L2 15 S L1
L3 238 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 23:32:34 ON 29 MAR 2004

L4 11 S L3
L5 2 S L4 AND DUMAS, J?/AU
L6 9 S L4 NOT L5
L7 0 S L6 AND KHIRE, U?/AU
L8 1 S L6 AND LOWINGER, T?/AU
L9 8 S L6 NOT L8
L10 0 S L9 AND PAULSEN, H?/AU
L11 0 S L9 AND RIEDL, B?/AU
L12 0 S L9 AND SCOTT, W?/AU
L13 0 S L9 AND SMITH, R?/AU
L14 0 S L9 AND WOOD, J?/AU
L15 0 S L9 AND HATOUM-MOKDAD, H?/AU
L16 0 S L9 AND JOHNSON, W?/AU
L17 0 S L9 AND LEE, W?/AU
L18 0 S L9 AND REDMAN, A?/AU
L19 0 S L9 AND SIBLEY, R?/AU
L20 0 S L9 AND RENICK, J?/AU

FILE 'CAOLD' ENTERED AT 23:36:53 ON 29 MAR 2004

L21 0 S L3

FILE 'REGISTRY' ENTERED AT 23:37:00 ON 29 MAR 2004

L22 STRUCTURE UPLOADED
L23 4 S L22

L24 110 S L22 FULL

FILE 'HCAPLUS' ENTERED AT 23:38:41 ON 29 MAR 2004

L25 7 S L24
 L26 2 S L25 AND DUMAS, J?/AU
 L27 5 S L25 NOT L26
 L28 0 S L27 AND KHIRE, U?/AU
 L29 0 S L27 AND LOWINGER, T?/AU
 L30 0 S L27 AND PAULSEN, H?/AU
 L31 0 S L27 AND RIEDL, B?/AU
 L32 0 S L27 AND SCOTT, W?/AU
 L33 0 S L27 AND SMITH, R?/AU
 L34 0 S L27 AND WOOD, J?/AU
 L35 0 S L27 AND HATOUM-MOKDAD, H?/AU
 L36 0 S L27 AND JOHNSON, J?/AU
 L37 0 S L27 AND LEE, W?/AU
 L38 0 S L27 AND REDMAN, A?/AU
 L39 0 S L27 AND SIBLEY, R?/AU
 L40 0 S L27 AND RENICK, J?/AU

=> s l24

L41 7 L24

=> file caold

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	45.09	427.50
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
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FILE COVERS 1907-1966

FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REGISTRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

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(FILE 'HOME' ENTERED AT 23:30:16 ON 29 MAR 2004)

FILE 'REGISTRY' ENTERED AT 23:30:21 ON 29 MAR 2004

L1 STRUCTURE UPLOADED
 L2 15 S L1
 L3 238 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 23:32:34 ON 29 MAR 2004

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L5      2 S L4 AND DUMAS, J?/AU
L6      9 S L4 NOT L5
L7      0 S L6 AND KHIRE, U?/AU
L8      1 S L6 AND LOWINGER, T?/AU
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L20     0 S L9 AND RENICK, J?/AU

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FILE 'CAOLD' ENTERED AT 23:36:53 ON 29 MAR 2004

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L21     0 S L3

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FILE 'REGISTRY' ENTERED AT 23:37:00 ON 29 MAR 2004

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L22     STRUCTURE UPLOADED
L23     4 S L22
L24     110 S L22 FULL

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FILE 'HCAPLUS' ENTERED AT 23:38:41 ON 29 MAR 2004

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L25     7 S L24
L26     2 S L25 AND DUMAS, J?/AU
L27     5 S L25 NOT L26
L28     0 S L27 AND KHIRE, U?/AU
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L41     7 S L24

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FILE 'CAOLD' ENTERED AT 23:41:36 ON 29 MAR 2004

=> s 124

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L42     1 L24

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=> d 142, all, 1

L42 ANSWER 1 OF 1 CAOLD COPYRIGHT 2004 ACS on STN

AN CA53:6122i CAOLD

TI synthesis of asym. substituted derivs. of thiourea with potential
tuberculostatic activity

AU Oeriu, Simion; Voinescu, M.; Wexler, B.; Gloter, E.

IT 1138-72-3 1142-30-9 100615-38-1 100720-16-9 100875-53-4 100875-54-5
101264-75-9 101872-56-4

=> fil reg; d acc 100720-16-9; fil CAOLD

FILE 'REGISTRY' ENTERED AT 23:41:53 ON 29 MAR 2004

ANSWER 1 REGISTRY COPYRIGHT 2004 ACS on STN

RN 100720-16-9 REGISTRY

CN Urea, 1-(3,4-dimethyl-5-isoxazolyl)-3-(p-ethoxyphenyl)-2-thio- (6CI) (CA
INDEX NAME)

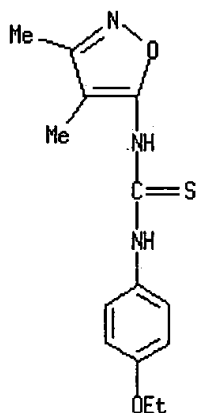
FS 3D CONCORD

MF C14 H17 N3 O2 S

SR CAOLD

LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS

(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

FILE 'CAOLD' ENTERED AT 23:41:54 ON 29 MAR 2004

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COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	0.42	431.15
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	0.00	-12.47

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